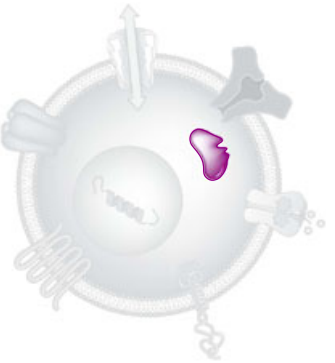
THE CONCISE GUIDE TO PHARMACOLOGY 2017/18: Enzymes

Stephen PH Alexander[1], Doriano Fabbro[2], Eamonn Kelly[3], Neil V Marrion[3], John A Peters[4], Elena Faccenda[5], Simon D Harding[5], Adam J Pawson[5], Joanna L Sharman[5], Christopher Southan[5], Jamie A Davies[5] and CGTP Collaborators

[1]*School of Life Sciences, University of Nottingham Medical School, Nottingham, NG7 2UH, UK*
[2]*PIQUR Therapeutics, Basel 4057, Switzerland*
[3]*School of Physiology, Pharmacology and Neuroscience, University of Bristol, Bristol, BS8 1TD, UK*
[4]*Neuroscience Division, Medical Education Institute, Ninewells Hospital and Medical School, University of Dundee, Dundee, DD1 9SY, UK*
[5]*Centre for Integrative Physiology, University of Edinburgh, Edinburgh, EH8 9XD, UK*



Abstract

The Concise Guide to PHARMACOLOGY 2017/18 provides concise overviews of the key properties of nearly 1800 human drug targets with an emphasis on selective pharmacology (where available), plus links to an open access knowledgebase of drug targets and their ligands (www.guidetopharmacology.org), which provides more detailed views of target and ligand properties. Although the Concise Guide represents approximately 400 pages, the material presented is substantially reduced compared to information and links presented on the website. It provides a permanent, citable, point-in-time record that will survive database updates. The full contents of this section can be found at http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full. Enzymes are one of the eight major pharmacological targets into which the Guide is divided, with the others being: G protein-coupled receptors, ligand-gated ion channels, voltage-gated ion channels, other ion channels, nuclear hormone receptors, catalytic receptors and transporters. These are presented with nomenclature guidance and summary information on the best available pharmacological tools, alongside key references and suggestions for further reading. The landscape format of the Concise Guide is designed to facilitate comparison of related targets from material contemporary to mid-2017, and supersedes data presented in the 2015/16 and 2013/14 Concise Guides and previous Guides to Receptors and Channels. It is produced in close conjunction with the Nomenclature Committee of the Union of Basic and Clinical Pharmacology (NC-IUPHAR), therefore, providing official IUPHAR classification and nomenclature for human drug targets, where appropriate.

Conflict of interest

The authors state that there are no conflicts of interest to declare.

Overview: Enzymes are protein catalysts facilitating the conversion of substrates into products. The Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (NC-IUBMB) classifies enzymes into families, using a four number code, on the basis of the reactions they catalyse. There are six main families:

EC 1.-.-.- Oxidoreductases;
EC 2.-.-.- Transferases;
EC 3.-.-.- Hydrolases;
EC 4.-.-.- Lyases;
EC 5.-.-.- Isomerases;
EC 6.-.-.- Ligases.

Although there are many more enzymes than receptors in biology, and many drugs that target prokaryotic enzymes are effective medicines, overall the number of enzyme drug targets is relatively small [392, 430], which is not to say that they are of modest importance.

The majority of drugs which act on enzymes act as inhibitors; one exception is metformin, which appears to stimulate activity of AMP-activated protein kinase, albeit through an imprecisely-defined mechanism. Kinetic assays allow discrimination of competitive, non-competitive, and un-competitive inhibitors. The majority of inhibitors are competitive (acting at the enzyme's ligand recognition site), non-competitive (acting at a distinct site; potentially interfering with co-factor or co-enzyme binding) or of mixed type. One rare example of an uncompetitive inhibitor is lithium ions, which are effective inhibitors at inositol monophosphatase only in the presence of high substrate concentrations. Some inhibitors are irreversible, including a group known as suicide substrates, which bind to the ligand recognition site and then couple covalently to the enzyme. It is beyond the scope of the Guide to give mechanistic information about the inhibitors described, although generally this information is available from the indicated literature.

Many enzymes require additional entities for functional activity. Some of these are used in the catalytic steps, while others pro-

mote a particular conformational change. Co-factors are tightly bound to the enzyme and include metal ions and heme groups. Co-enzymes are typically small molecules which accept or donate functional groups to assist in the enzymatic reaction. Examples include ATP, NAD, NADP and S-adenosylmethionine, as well as a number of vitamins, such as riboflavin (vitamin B1) and thiamine (vitamin B2). Where co-factors/co-enzymes have been identified, the Guide indicates their involvement.

Family structure

S275 Kinases (EC 2.7.x.x)
– AGC: Containing PKA, PKG, PKC families
– DMPK family
– GEK subfamily
– Other DMPK family kinases
S276 Rho kinase
– G protein-coupled receptor kinases (GRKs)
– Beta-adrenergic receptor kinases (βARKs)
– Opsin/rhodopsin kinases
– GRK4 subfamily
– MAST family
– NDR family
– PDK1 family
– Protein kinase A
– Akt (Protein kinase B)
S276 Protein kinase C (PKC)
S277 Alpha subfamily
S277 Delta subfamily
S277 Eta subfamily
– Iota subfamily
– Protein kinase G (PKG)
– Protein kinase N (PKN) family
– RSK family
– MSK subfamily
– p70 subfamily
– RSK subfamily
– RSKR subfamily
– RSKL family
– SGK family
– YANK family
– Atypical
– ABC1 family
– ABC1-A subfamily
– ABC1-B subfamily
– Alpha kinase family
– ChaK subfamily
– eEF2K subfamily
– Other alpha kinase family kinases
– BCR family
– Bromodomain kinase (BRDK) family
– G11 family
– Phosphatidyl inositol 3′ kinase-related kinases (PIKK) family
– ATR subfamily
S278 FRAP subfamily
– SMG1 subfamily
– TRRAP subfamily
– Other PIKK family kinases
– RIO family
– RIO1 subfamily
– RIO2 subfamily
– RIO3 subfamily
– PDHK family
– Pyruvate dehydrogenase kinase (PDHK) family
– TAF1 family
– TIF1 family
CAMK: Calcium/calmodulin-dependent protein kinases
– CAMK1 family
– CAMK2 family
– CAMK-like (CAMKL) family
– AMPK subfamily
– BRSK subfamily
– CHK1 subfamily
– HUNK subfamily
– LKB subfamily
– MARK subfamily
– MELK subfamily
– NIM1 subfamily
– NuaK subfamily
– PASK subfamily
– QIK subfamily
– SNRK subfamily
– CAMK-unique family
– CASK family
– DCAMKL family
– Death-associated kinase (DAPK) family
– MAPK-Activated Protein Kinase (MAPKAPK) family
– MAPKAPK subfamily
– MKN subfamily
– Myosin Light Chain Kinase (MLCK) family
– Phosphorylase kinase (PHK) family
– PIM family
– Protein kinase D (PKD) family
– PSK family
– RAD53 family
– Testis specific kinase (TSSK) family
– Trbl family
– Trio family
CK1: Casein kinase 1
– Casein kinase 1 (CK1) family
– Tau tubulin kinase (TTBK) family
– Vaccina related kinase (VRK) family
CMGC: Containing CDK, MAPK, GSK3, CLK families
– CLK family
S279 Cyclin-dependent kinase (CDK) family
– CCRK subfamily
CDK1 subfamily
S279 CDK4 subfamily
– CDK5 subfamily
– CDK7 subfamily
– CDK8 subfamily
– CDK9 subfamily
– CDK10 subfamily
– CRK7 subfamily
– PITSLRE subfamily
– TAIRE subfamily
Cyclin-dependent kinase-like (CDKL) family
Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase (DYRK) family
– Dyrk1 subfamily
– Dyrk2 subfamily
– HIPK subfamily
– PRP4 subfamily
Glycogen synthase kinase (GSK) family
S279 GSK subfamily
Mitogen-activated protein kinases (MAP kinases)
– ERK subfamily
– Erk7 subfamily
– JNK subfamily
– p38 subfamily
– nmo subfamily
RCK family
SRPK family
Other protein kinases
– CAMKK family

Kinases (EC 2.7.x.x)

Enzymes → Kinases (EC 2.7.x.x)

Overview: Protein kinases (E.C. 2.7.11.-) use the co-substrate ATP to phosphorylate serine and/or threonine residues on target proteins. Analysis of the human genome suggests the presence of 518 protein kinases in man (divided into 15 subfamilies), with over 100 protein kinase-like pseudogenes [335]. It is beyond the scope of the Concise Guide to list all these protein kinase activities, but full listings are available on the 'Detailed page' provided for each enzyme.

Most inhibitors of these enzymes have been assessed in cell-free investigations and so may appear to 'lose' potency and selectivity in intact cell assays. In particular, ambient ATP concentrations may be influential in responses to inhibitors, since the majority are directed at the ATP binding site [110] .

Rho kinase

Enzymes → Kinases (EC 2.7.x.x) → AGC: Containing PKA, PKG, PKC families → DMPK family → Rho kinase

Overview: Rho kinase (also known as P160ROCK, Rho-activated kinase) is activated by members of the Rho small G protein family, which are activated by GTP exchange factors, such as *ARHGEF1* (Q92888, p115-RhoGEF), which in turn may be activated by $G\alpha_{12/13}$ subunits [282].

Nomenclature	Rho associated coiled-coil containing protein kinase 1	Rho associated coiled-coil containing protein kinase 2
Systematic nomenclature	ROCK1	ROCK2
HGNC, UniProt	*ROCK1*, Q13464	*ROCK2*, O75116
EC number	2.7.11.1	2.7.11.1
Common abreviation	Rho kinase 1	Rho kinase 2
Inhibitors	RKI-1447 (pIC_{50} >9) [414], Y27632 (pIC_{50} 5.9–7.3) [328, 575], fasudil (pK_i 7) [434], Y27632 (pK_i 6.8) [540], fasudil (pIC_{50} 5.5–5.6) [328, 434]	RKI-1447 (pIC_{50} >9) [414], compound 11d [DOI: 10.1039/c0md00194e] (pIC_{50} >9) [90], GSK269962A (pIC_{50} 8.4) [126], compound 32 (pIC_{50} 8.4) [49], compound 22 (pIC_{50} 7.7) [575], Y27632 (pIC_{50} 6.3–7.2) [328, 575], Y27632 (pK_i 6.8–6.9) [328, 540], fasudil (pIC_{50} 5.9–5.9) [328, 434]
Selective inhibitors	GSK269962A (pIC_{50} 8.8) [126]	–

Further reading on Rho kinases

Feng, Y, PV LoGrasso, O Defert and R Li 2016 Rho Kinase (ROCK) Inhibitors and Their Therapeutic Potential J Med Chem 59: 2269-300 [PMID:26486225]

Nishioka, T, MH Shohag, M Amano and K Kaibuchi 2015 Developing novel methods to search for substrates of protein kinases such as Rho-kinase Biochim Biophys Acta 1854: 1663-6 [PMID:25770685]

Shimokawa, H, S Sunamura and K Satoh 2016 RhoA/Rho-Kinase in the Cardiovascular System Circ Res 118: 352-66 [PMID:26838319]

Protein kinase C (PKC)

Enzymes → Kinases (EC 2.7.x.x) → AGC: Containing PKA, PKG, PKC families → Protein kinase C (PKC)

Overview: Protein kinase C is the target for the tumour-promoting phorbol esters, such as tetradecanoyl-β-phorbol acetate (TPA, also known as phorbol 12-myristate 13-acetate).

Classical protein kinase C isoforms: **PKCα, PKCβ, and PKCγ** are activated by Ca^{2+} and diacylglycerol, and may be inhibited by GF109203X, calphostin C, Gö 6983, chelerythrine and Ro31-8220.

Novel protein kinase C isoforms: **PKCδ, PKCε, PKCη, PKCϑ and PKCμ** are activated by diacylglycerol and may be inhibited by calphostin C, Gö 6983 and chelerythrine.

*Atypical protein kinase C isoforms:***PKCι, PKCζ**.

Alpha subfamily

Enzymes → Kinases (EC 2.7.x.x) → AGC: Containing PKA, PKG, PKC families → Protein kinase C (PKC) → Alpha subfamily

Nomenclature	protein kinase C beta	protein kinase C gamma
HGNC, UniProt	*PRKCB*, P05771	*PRKCG*, P05129
EC number	2.7.11.13	2.7.11.13
Common abreviation	PKCβ	PKCγ
Inhibitors	sotrastaurin (pIC_{50} 8.7) [548], Gö 6983 (pIC_{50} 8.1) [195], GF109203X (pIC_{50} 7.8) [533] – Bovine, 7-hydroxystaurosporine (pIC_{50} 7.5) [468]	Gö 6983 (pIC_{50} 8.2) [195], 7-hydroxystaurosporine (pIC_{50} 7.5) [469]
Selective inhibitors	ruboxistaurin (pIC_{50} 8.2) [250], enzastaurin (pIC_{50} 7.5) [140], CGP53353 (pIC_{50} 6.4) [75]	–

Delta subfamily

Enzymes → Kinases (EC 2.7.x.x) → AGC: Containing PKA, PKG, PKC families → Protein kinase C (PKC) → Delta subfamily

Nomenclature	protein kinase C alpha	protein kinase C delta
HGNC, UniProt	*PRKCA*, P17252	*PRKCD*, Q05655
EC number	2.7.11.13	2.7.11.13
Common abreviation	PKCα	PKCδ
Activators	–	ingenol mebutate (pK_i 9.4) [263]
Inhibitors	sotrastaurin (pIC_{50} 8.7) [548], Gö 6983 (pIC_{50} 8.1) [195], 7-hydroxystaurosporine (pIC_{50} 7.5) [468]	sotrastaurin (pIC_{50} 8.9) [548], Gö 6983 (pIC_{50} 8) [195]

Eta subfamily

Enzymes → Kinases (EC 2.7.x.x) → AGC: Containing PKA, PKG, PKC families → Protein kinase C (PKC) → Eta subfamily

Nomenclature	protein kinase C epsilon
HGNC, UniProt	*PRKCE*, Q02156
EC number	2.7.11.13
Common abreviation	PKCϵ
Inhibitors	sotrastaurin (pIC_{50} 8.2) [548]

Further reading on Protein kinase C

Igumenova TI. (2015) Dynamics and Membrane Interactions of Protein Kinase C. *Biochemistry* **54**: 4953-68 [PMID:26214365]

Newton AC *et al.* (2017) Reversing the Paradigm: Protein Kinase C as a Tumor Suppressor. *Trends Pharmacol Sci* **38**: 438-447 [PMID:28283201]

Salzer E *et al.* (2016) Protein Kinase C delta: a Gatekeeper of Immune Homeostasis. *J Clin Immunol* **36**: 631-40 [PMID:27541826]

FRAP subfamily

Enzymes → Kinases (EC 2.7.x.x) → Atypical → Phosphatidyl inositol 3′ kinase-related kinases (PIKK) family → FRAP subfamily

Nomenclature	mechanistic target of rapamycin
HGNC, UniProt	*MTOR*, P42345
EC number	2.7.11.1
Common abreviation	mTOR
Inhibitors	ridaforolimus (pIC_{50} 9.7) [441], torin 1 (pIC_{50} 9.5) [310], INK-128 (pIC_{50} 9) [231], INK-128 (pK_i 8.9) [231], gedatolisib (pIC_{50} 8.8) [544], dactolisib (pIC_{50} 8.2) [332], PP-242 (pIC_{50} 8.1) [15], PP121 (pIC_{50} 8) [15], XL388 (pIC_{50} 8) [511], PF-04691502 (pK_i 7.8) [309], apitolisib (pK_i 7.8) [506]
Selective inhibitors	everolimus (pIC_{50} 8.7) [464], temsirolimus (pIC_{50} 5.8) [278]

Further reading on FRAP subfamily

Hukelmann JL *et al.* (2016) The cytotoxic T cell proteome and its shaping by the kinase mTOR. *Nat. Immunol.* **17**: 104-12 [PMID:26551880]

Saxton RA *et al.* (2017) mTOR Signaling in Growth, Metabolism, and Disease. *Cell* **169**: 361-371 [PMID:28388417]

Cyclin-dependent kinase (CDK) family

Enzymes → Kinases (EC 2.7.x.x) → CMGC: Containing CDK, MAPK, GSK3, CLK families → Cyclin-dependent kinase (CDK) family

Overview: The development of CDK inhibitors as anticancer drugs is reviewed in [508], with detailed content covering CDK4 and CDK6 inhibitors under clinical evaluation.

CDK4 subfamily

Enzymes → Kinases (EC 2.7.x.x) → CMGC: Containing CDK, MAPK, GSK3, CLK families → Cyclin-dependent kinase (CDK) family → CDK4 subfamily

Nomenclature	cyclin dependent kinase 4	cyclin dependent kinase 6
HGNC, UniProt	*CDK4*, P11802	*CDK6*, Q00534
EC number	2.7.11.22	2.7.11.22
Common abreviation	CDK4	CDK6
Inhibitors	R547 (pK_i 9) [117], palbociclib (pIC_{50} 8) [160], Ro-0505124 (pIC_{50} 7.7) [129], riviciclib (pIC_{50} 7.2) [258], alvocidib (pK_i 7.2) [70]	palbociclib (pIC_{50} 7.8) [160]

GSK subfamily

Enzymes → Kinases (EC 2.7.x.x) → CMGC: Containing CDK, MAPK, GSK3, CLK families → Glycogen synthase kinase (GSK) family → GSK subfamily

Nomenclature	glycogen synthase kinase 3 beta
HGNC, UniProt	*GSK3B*, P49841
EC number	2.7.11.26
Common abreviation	GSK3B
Inhibitors	CHIR-98014 (pIC_{50} 9.2) [440], LY2090314 (pIC_{50} 9) [133], CHIR-99021 (pIC_{50} 8.2) [440], SB 216763 (pIC_{50} ~8.1) [95], 1-azakenpaullone (pIC_{50} 7.7) [285], SB-415286 (pIC_{50} ~7.4) [95], IM-12 (pIC_{50} 7.3) [460]
Selective inhibitors	AZD2858 (pK_i 8.3) [31]
Comments	Due to its Tau phosphorylating activity, small molecule inhibitors of GSK-3β are being investigated as potential treatments for Alzheimer's disease (AD) [31]. GSK-3β also plays a role in canonical Wnt pathway signalling, the normal activity of which is crucial for the maintenance of normal bone mass. It is hypothesised that small molecule inhibitors of GSK-3β may provide effective therapeutics for the treatment of diseases characterised by low bone mass [320].

Further reading on GSK subfamily

Beurel E *et al.* (2015) Glycogen synthase kinase-3 (GSK3): regulation, actions, and diseases. *Pharmacol Ther* **148**: 114-31 [PMID:25435019]
Domoto T *et al.* (2016) Glycogen synthase kinase-3beta is a pivotal mediator of cancer invasion and resistance to therapy. *Cancer Sci* **107**: 1363-1372 [PMID:27486911]
Khan I *et al.* (2017) Natural and synthetic bioactive inhibitors of glycogen synthase kinase. *Eur J Med Chem* **125**: 464-477 [PMID:27689729]
Maqbool M *et al.* (2016) Pivotal role of glycogen synthase kinase-3: A therapeutic target for Alzheimer's disease. *Eur J Med Chem* **107**: 63-81 [PMID:26562543]

Polo-like kinase (PLK) family

Enzymes → Kinases (EC 2.7.x.x) → Other protein kinases → Polo-like kinase (PLK) family

Nomenclature	polo like kinase 4
HGNC, UniProt	*PLK4*, O00444
EC number	2.7.11.21
Common abreviation	PLK4
Inhibitors	CFI-400945 (pIC_{50} 8.6) [343]

STE7 family

Enzymes → Kinases (EC 2.7.x.x) → STE: Homologs of yeast Sterile 7, Sterile 11, Sterile 20 kinases → STE7 family

Nomenclature	mitogen-activated protein kinase kinase 1	mitogen-activated protein kinase kinase 2
HGNC, UniProt	*MAP2K1*, Q02750	*MAP2K2*, P36507
EC number	2.7.12.2	2.7.12.2
Common abreviation	MEK1	MEK2
Inhibitors	trametinib (pIC_{50} 9–9.1) [183, 589], PD 0325901 (pIC_{50} 8.1) [208]	trametinib (pIC_{50} 8.7) [589]
Allosteric modulators	binimetinib (Negative) (pIC_{50} 7.9) [428], refametinib (Negative) (pIC_{50} 7.7) [242], CI-1040 (Negative) (pK_d 6.9) [112]	binimetinib (Negative) (pIC_{50} 7.9) [428], refametinib (Negative) (pIC_{50} 7.3) [242]
Selective allosteric modulators	cobimetinib (Negative) (pIC_{50} 9.1) [457]	–

Abl family

Enzymes → Kinases (EC 2.7.x.x) → TK: Tyrosine kinase → Non-receptor tyrosine kinases (nRTKs) → Abl family

Nomenclature	ABL proto-oncogene 1, non-receptor tyrosine kinase
HGNC, UniProt	*ABL1*, P00519
EC number	2.7.10.2
Common abreviation	Abl
Inhibitors	compound 8h (pIC_{50} 9.7) [529], dasatinib (pIC_{50} 9.6) [270], compound 24 (pIC_{50} 9.3) [118], PD-173955 (pK_d 9.2) [112], bosutinib (pIC_{50} 9) [186], PD-173955 (pIC_{50} ~8.3) [362], bafetinib (pIC_{50} 7.6–8.2) [228, 269], ponatinib (pIC_{50} 8.1) [232], nilotinib (pIC_{50} 7.8) [372], PP121 (pIC_{50} 7.7) [15], imatinib (pIC_{50} 6.7) [228], GNF-5 (pIC_{50} 6.7) [597]

Ack family

Enzymes → Kinases (EC 2.7.x.x) → TK: Tyrosine kinase → Non-receptor tyrosine kinases (nRTKs) → Ack family

Nomenclature	tyrosine kinase non receptor 2
HGNC, UniProt	*TNK2*, Q07912
EC number	2.7.10.2
Common abreviation	Ack
Inhibitors	compound 30 (pIC_{50} 9) [122]

Janus kinase (JakA) family

Enzymes → Kinases (EC 2.7.x.x) → TK: Tyrosine kinase → Non-receptor tyrosine kinases (nRTKs) → Janus kinase (JakA) family

Nomenclature	Janus kinase 1	Janus kinase 2	Janus kinase 3	tyrosine kinase 2
HGNC, UniProt	*JAK1*, P23458	*JAK2*, O60674	*JAK3*, P52333	*TYK2*, P29597
EC number	2.7.10.2	2.7.10.2	2.7.10.2	2.7.10.2
Common abreviation	JAK1	JAK2	JAK3	Tyk2

(continued)				
Nomenclature	Janus kinase 1	Janus kinase 2	Janus kinase 3	tyrosine kinase 2
Inhibitors	ruxolitinib (pIC_{50} 8.5–10.1) [203, 423], filgotinib (pIC_{50} 8) [541]	NS-018 (pIC_{50} 9.1) [374], BMS-911543 (pIC_{50} 9) [420], AT-9283 (pIC_{50} 8.9) [230], XL019 (pIC_{50} 8.7) [152], fedratinib (pIC_{50} 8.5) [333, 566], gandotinib (pIC_{50} 8.4) [330]	AT-9283 (pIC_{50} 9) [230]	–
Selective inhibitors	–	compound 1d (pIC_{50} >9) [554]	–	–
Comments	–	The $JAK2^{V617F}$ mutation, which causes constitutive activation, plays an oncogenic role in the pathogenesis of the myeloproliferative disorders, polycythemia vera, essential thrombocythemia, and idiopathic myelofibrosis [64, 115]. Small molecule compounds which inhibit aberrant JAK2 activity are being developed as novel anti-cancer pharmaceuticals.	–	–

Src family

Enzymes → Kinases (EC 2.7.x.x) → TK: Tyrosine kinase → Non-receptor tyrosine kinases (nRTKs) → Src family

Nomenclature	BLK proto-oncogene, Src family tyrosine kinase	fyn related Src family tyrosine kinase	FYN proto-oncogene, Src family tyrosine kinase	LYN proto-oncogene, Src family tyrosine kinase	SRC proto-oncogene, non-receptor tyrosine kinase
HGNC, UniProt	*BLK*, P51451	*FRK*, P42685	*FYN*, P06241	*LYN*, P07948	*SRC*, P12931
EC number	2.7.10.2	2.7.10.2	2.7.10.2	2.7.10.2	2.7.10.2
Common abreviation	Blk	FRK	Fyn	Lyn	Src
Inhibitors	–	–	PP1 (pIC_{50} 8.2) [205]	bafetinib (pIC_{50} 8) [228]	WH-4-023 (pIC_{50} 8.2) [340], PD166285 (pK_i 8.1) [396], PP121 (pIC_{50} 7.8) [15], ENMD-2076 (pIC_{50} 7.7) [416]

Tec family

Enzymes → Kinases (EC 2.7.x.x) → TK: Tyrosine kinase → Non-receptor tyrosine kinases (nRTKs) → Tec family

Nomenclature	BMX non-receptor tyrosine kinase	Bruton tyrosine kinase	TXK tyrosine kinase
HGNC, UniProt	*BMX*, P51813	*BTK*, Q06187	*TXK*, P42681
EC number	2.7.10.2	2.7.10.2	2.7.10.2
Common abreviation	Etk	Btk	TXK
Inhibitors	compound 38 (pIC_{50} 9.1) [300], ibrutinib (pIC_{50} 9.1) [318], compound 31 (pIC_{50} 8.7) [300]	ibrutinib (pIC_{50} 9.3) [395], compound 31 (pIC_{50} 8.4) [300], compound 38 (pIC_{50} >8.4) [300]	–
Selective inhibitors	BMX-IN-1 (pIC_{50} 8.1) [307]	CGI1746 (pIC_{50} 8.7) [120], CHMFL-BTK-11 (Irreversible inhibition) (pIC_{50} 7.6) [576]	–

RAF family

Enzymes → Kinases (EC 2.7.x.x) → TKL: Tyrosine kinase-like → RAF family

Nomenclature	B-Raf proto-oncogene, serine/threonine kinase	Raf-1 proto-oncogene, serine/threonine kinase
HGNC, UniProt	*BRAF*, P15056	*RAF1*, P04049
EC number	2.7.11.1	2.7.11.1
Common abreviation	B-Raf	c-Raf
Inhibitors	GDC-0879 (pIC_{50} 9.7–9.9) [112, 206], dabrafenib (pIC_{50} 8.5) [305], regorafenib (pIC_{50} 7.6) [594], vemurafenib (pIC_{50} 7) [555], PLX-4720 (pK_d 6.5) [112], compound 2 (pK_d 6.3) [227], CHIR-265 (pK_d 5.9) [112]	–
Selective inhibitors	–	GW5074 (pIC_{50} 8.1) [88]

Further reading on Kinases (EC 2.7.x.x)

Eglen R *et al.* (2011) Drug discovery and the human kinome: recent trends. *Pharmacol. Ther.* **130**: 144-56 [PMID:21256157]
Graves LM *et al.* (2013) The dynamic nature of the kinome. *Biochem. J.* **450**: 1-8 [PMID:23343193]
Liu Q *et al.* (2013) Developing irreversible inhibitors of the protein kinase cysteinome. *Chem. Biol.* **20**: 146-59 [PMID:23438744]
Martin KJ *et al.* (2012) Selective kinase inhibitors as tools for neuroscience research. *Neuropharmacology* **63**: 1227-37 [PMID:22846224]
Tarrant MK *et al.* (2009) The chemical biology of protein phosphorylation. *Annu. Rev. Biochem.* **78**: 797-825 [PMID:19489734]
Wu-Zhang AX *et al.* (2013) Protein kinase C pharmacology: refining the toolbox. *Biochem. J.* **452**: 195-209 [PMID:23662807]

Peptidases and proteinases

Enzymes → Peptidases and proteinases

Overview: Peptidases and proteinases hydrolyse peptide bonds, and can be simply divided on the basis of whether terminal peptide bonds are cleaved (exopeptidases and exoproteinases) at the amino terminus (aminopeptidases) or carboxy terminus (carboxypeptidases). Non-terminal peptide bonds are cleaved by endopeptidases and endoproteinases, which are divided into serine endopeptidases (EC 3.4.21.-), cysteine endopeptidases (EC 3.4.22.-), aspartate endopeptidases (EC 3.4.23.-), metalloendopeptidases (EC 3.4.24.-) and threonine endopeptidases (EC 3.4.25.-).
Since it is beyond the scope of the Guide to list all peptidase and proteinase activities, this summary focuses on selected enzymes of significant pharmacological interest that have ligands (mostly small-molecules) directed against them. For those interested in detailed background we recommend the MEROPS database [450] (with whom we collaborate) as an information resource [432].

A1: Pepsin

Enzymes → Peptidases and proteinases → AA: Aspartic (A) Peptidases → A1: Pepsin

Nomenclature	renin
HGNC, UniProt	*REN*, P00797
EC number	3.4.23.15
Inhibitors	aliskiren (pIC_{50} 9.2) [580]

A22: Presenilin

Enzymes → Peptidases and proteinases → AD: Aspartic (A) Peptidases → A22: Presenilin

Overview: Presenilin (PS)-1 or -2 act as the catalytic component/essential co-factor of the γ-secretase complex responsible for the final carboxy-terminal cleavage of amyloid precursor protein (APP) [260] in the generation of amyloid beta (Aβ) [7, 510]. Given that the accumulation and aggregation of Aβ in the brain is pivotal in the development of Alzheimer's disease (AD), inhibition of PS activity is one mechanism being investigated as a therapeutic option for AD [187]. Several small molecule inhibitors of PS-1 have been investigated, with some reaching early clinical trials, but none have been formally approved. Dewji *et al.* (2015) have reported that small peptide fragments of human PS-1 can significantly inhibit Aβ production (total Aβ, Aβ40 and Aβ42) both *in vitro* and when infused in to the brains of APP transgenic mice [119]. The most active small peptides in this report were P4 and P8, from the amino-terminal domain of PS-1.

Information on members of this family may be found in the online database.

C14: Caspase

Enzymes → Peptidases and proteinases → CD: Cysteine (C) Peptidases → C14: Caspase

Overview: Caspases, (E.C. 3.4.22.-) which derive their name from Cysteine ASPartate-specific proteASES, include at least two families; initiator caspases (caspases 2, 8, 9 and 10), which are able to hydrolyse and activate a second family of effector caspases (caspases 3, 6 and 7), which themselves are able to hydrolyse further cellular proteins to bring about programmed cell death. Caspases are heterotetrameric, being made up of two pairs of subunits, generated by a single gene product, which is proteolysed to form the mature protein. Members of the mammalian inhibitors of apoptosis proteins (IAP) are able to bind the procaspases, thereby preventing maturation to active proteinases.

Information on members of this family may be found in the online database.

Comments: CARD16 (Caspase recruitment domain-containing protein 16, caspase-1 inhibitor COP, CARD only domain-containing protein 1, pseudo interleukin-1β converting enzyme, pseudo-ICE, ENSG00000204397) shares sequence similarity with some of the caspases.

M1: Aminopeptidase N

Enzymes → Peptidases and proteinases → MA: Metallo (M) Peptidases → M1: Aminopeptidase N

Overview: Aminopeptidases catalyze the cleavage of amino acids from the amino (N) terminus of protein or peptide substrates, and are involved in many essential cellular functions. Members of this enzyme family may be monomeric or multi-subunit complexes, and many are zinc metalloenzymes [522].

Information on members of this family may be found in the online database.

M2: Angiotensin-converting (ACE and ACE2)

Enzymes → Peptidases and proteinases → MA: Metallo (M) Peptidases → M2: Angiotensin-converting (ACE and ACE2)

Nomenclature	Angiotensin-converting enzyme
HGNC, UniProt	*ACE*, P12821
EC number	3.4.15.1
Common abreviation	ACE
Endogenous substrates	angiotensin I (*AGT*, P01019) > angiotensin II (*AGT*, P01019)
Inhibitors	zofenoprilat (pK_i 9.4) [283] – Rabbit, captopril (pK_i 8.4) [354], zofenopril
Selective inhibitors	perindoprilat (pIC_{50} 9) [73], cilazaprilat (pIC_{50} 8.7) [559] – Rabbit, imidaprilat (pIC_{50} 8.7) [443], lisinopril-tryptophan (C-domain assay) (pIC_{50} 8.2) [560], RXP-407 (N-domain selective inhibition) (pIC_{50} 8.1) [472], fosinoprilat (pIC_{50} 8) [113] – Rabbit, enalaprilat (pIC_{50} 7.5) [87], benazeprilat (pIC_{50} 6.6) [296]
Comments	Reports of ACE GPI hydrolase activity [277] have been refuted [298]

M10: Matrix metallopeptidase

Enzymes → Peptidases and proteinases → MA: Metallo (M) Peptidases → M10: Matrix metallopeptidase

Overview: Matrix metalloproteinases (MMP) are calcium- and zinc-dependent proteinases regulating the extracellular matrix and are often divided (*e.g.* [545]) on functional and structural bases into gelatinases, collagenases, stromyelinases and matrilysins, as well as membrane type-MMP (MT-MMP).

Nomenclature	MMP2	MMP8
HGNC, UniProt	*MMP2*, P08253	*MMP8*, P22894
EC number	3.4.24.24	3.4.24.34
Selective inhibitors	ARP100 [537]	–
Comments	MMP2 is categorised as a gelatinase with substrate specificity for gelatinase A.	MMP8 is categorised as a collagenase.

Comments: A number of small molecule 'broad spectrum' inhibitors of MMP have been described, including marimastat and batimastat.
Tissue inhibitors of metalloproteinase (TIMP) proteins are endogenous inhibitors acting to chelate MMP proteins: TIMP1 (*TIMP1*, P01033), TIMP2 (*TIMP2*, P16035), TIMP3 (*TIMP3*, P35625), TIMP4 (*TIMP4*, Q99727)

M12: Astacin/Adamalysin

Enzymes → Peptidases and proteinases → MA: Metallo (M) Peptidases → M12: Astacin/Adamalysin

Overview: ADAM (A Disintegrin And Metalloproteinase domain containing proteins) metalloproteinases cleave cell-surface or transmembrane proteins to generate soluble and membrane-limited products.
ADAMTS (with thrombospondin motifs) metalloproteinases cleave cell-surface or transmembrane proteins to generate soluble and membrane-limited products.

Information on members of this family may be found in the online database.

Comments: Additional ADAM family members include AC123767.2 (cDNA FLJ58962, moderately similar to mouse ADAM3, ENSG00000231168), AL160191.3 (ADAM21-like protein, ENSG00000235812), AC136428.3-2 (ENSG00000185520) and ADAMDEC1 (decysin 1, ENSG00000134028).
Other ADAMTS family members include AC104758.12-5 (FLJ00317 protein Fragment ENSG00000231463), AC139425.3-1 (ENSG00000225577), and AC126339.6-1 (ENSG00000225734).

M28: Aminopeptidase Y

Enzymes → Peptidases and proteinases → MH: Metallo (M) Peptidases → M28: Aminopeptidase Y

Nomenclature	Folate hydrolase (prostate-specific membrane antigen) 1
HGNC, UniProt	*FOLH1*, Q04609
EC number	3.4.17.21
Antibodies	capromab (Binding)
Comments	Folate hydrolase is also known as NAALADase as it is responsible for the hydrolysis of N-acetaspartylglutamate to form N-acetylaspartate and L-glutamate (L-glutamic acid). In the gut, the enzyme assists in the assimilation of folate by hydrolysing dietary poly-gamma-glutamylfolate. The enzyme is highly expressed in the prostate, and its expression is up-regulated in cancerous tissue. A tagged version of the antibody capromab has been used for imaging purposes.

Comments: Folate hydrolase is also known as NAALADase as it is responsible for the hydrolysis of N-acetaspartylglutamate to form N-acetylaspartate and L-glutamate. In the gut, the enzyme assists in the assimilation of folate by hydrolysing dietary poly-gamma-glutamylfolate. The enzyme is highly expressed in the prostate, and its expression is up-regulated in cancerous tissue. A tagged version of the antibody capromab has been used for imaging purposes.

M19: Membrane dipeptidase

Enzymes → Peptidases and proteinases → MJ: Metallo (M) Peptidases → M19: Membrane dipeptidase

Nomenclature	Dipeptidase 1
HGNC, UniProt	*DPEP1*, P16444
EC number	3.4.13.19: $LTD_4 + H_2O = LTE_4 + glycine$
Inhibitors	cilastatin (pK_i 6) [189]

S1: Chymotrypsin

Enzymes → Peptidases and proteinases → PA: Serine (S) Peptidases → S1: Chymotrypsin

Nomenclature	complement C1r	coagulation factor II, thrombin	coagulation factor X
HGNC, UniProt	*C1R*, P00736	*F2*, P00734	*F10*, P00742
EC number	3.4.21.41	3.4.21.5	3.4.21.6
Inhibitors	nafamostat (pIC_{50} 4.9) [216]	lepirudin (pK_i 13) [506], desirudin (pK_i 12.7) [254], AZ12971554 (pK_i 9.5) [19], melagatran (pK_i 8.7) [198], bivalirudin (pK_i 8.6) [573], dabigatran (pK_i 8.3) [211], argatroban (pK_i 7.7) [238]	rivaroxaban (pK_i 9.4) [407], edoxaban (pK_i 9.2) [412], apixaban (pK_i 9.1) [574]
Selective inhibitors	–	Dup-714 (pK_i 10.4) [175], AR-H067637 (pIC_{50} 8.4) [114]	–

Nomenclature	elastase, neutrophil expressed	plasminogen	plasminogen activator, tissue type	protease, serine 1	tryptase alpha/beta 1
HGNC, UniProt	*ELANE*, P08246	*PLG*, P00747	*PLAT*, P00750	*PRSS1*, P07477	*TPSAB1*, Q15661
EC number	3.4.21.37	3.4.21.7	3.4.21.68	3.4.21.4	3.4.21.59
Inhibitors	alvelestat (pK_i 8) [502], sivelestat (pIC_{50} 7.4) [103]	aprotinin {Bovine} (Binding) (pIC_{50} 6.8) [492], tranexamic acid (Binding) (pIC_{50} 3.6) [492]	–	nafamostat (pIC_{50} 7.8) [216]	nafamostat (pIC_{50} 10) [365]
Selective inhibitors	–	6-aminocaproic acid (Binding) (pIC_{50} 4.4) [86]	–	–	gabexate (pIC_{50} 8.5) [135]

T1: Proteasome

Enzymes → Peptidases and proteinases → PB: Threonine (T) Peptidases → T1: Proteasome

Overview: The T1 macropain beta subunits form the catalytic proteinase core of the 20S proteasome complex [93]. This catalytic core enables the degradation of peptides with Arg, Phe, Tyr, Leu, and Glu adjacent to the cleavage site. The β5 subunit is the principal target of the approved drug proteasome inhibitor bortezomib.

Nomenclature	proteasome subunit beta 5
HGNC, UniProt	*PSMB5*, P28074
EC number	3.4.25.1
Inhibitors	bortezomib (pIC_{50} 7.7) [371]
Selective inhibitors	ixazomib (pK_i 9) [286]

S8: Subtilisin

Enzymes → Peptidases and proteinases → SB: Serine (S) Peptidases → S8: Subtilisin

Overview: One member of this family has garnered intense interest as a clinical drug target. As liver PCSK9 acts to maintain cholesterol homeostasis, it has become a target of intense interest for clinical drug development. Inhibition of PCSK9 can lower low-density cholesterol (LDL-C) by clearing LDLR-bound LDL particles, thereby lowering circulating cholesterol levels. It is hypothesised that this action may improve outcomes in patients with atherosclerotic cardiovascular disease [315, 452, 501]. Therapeutics which inhibit PCSK9 are viewed as potentially lucrative replacements for statins, upon statin patent expiry. Several monoclonal antibodies including alirocumab, evolocumab, bococizumab, RG-7652 and LY3015014 are under development. One RNAi therapeutic, code named ALN-PCS02, is also in development [106, 147, 155].

Information on members of this family may be found in the online database.

S9: Prolyl oligopeptidase

Enzymes → Peptidases and proteinases → SC: Serine (S) Peptidases → S9: Prolyl oligopeptidase

Nomenclature	dipeptidyl peptidase 4
HGNC, UniProt	*DPP4*, P27487
EC number	3.4.14.5
Endogenous substrates	glucagon-like peptide 1 (*GCG*, P01275)
Inhibitors	saxagliptin (pK_i 9.2) [196], linagliptin (pK_i 9) [130], sitagliptin (pIC_{50} 8.1) [111], vildagliptin (pK_i 7.8) [196]

Acetylcholine turnover

Enzymes → Acetylcholine turnover

Overview: Acetylcholine is familiar as a neurotransmitter in the central nervous system and in the periphery. In the somatic nervous system, it activates nicotinic acetylcholine receptors at the skeletal neuromuscular junction. It is also employed in the autonomic nervous system, in both parasympathetic and sympathetic branches; in the former, at the smooth muscle neuromuscular junction, activating muscarinic acetylcholine receptors. In the latter, acetylcholine is involved as a neurotransmitter at the ganglion, activating nicotinic acetylcholine receptors. Acetylcholine is synthesised in neurones through the action of choline O-acetyltransferase and metabolised after release through the extracellular action of acetylcholinesterase and cholinesterase. Choline is accumulated from the extracellular medium by selective transporters (see SLC5A7 and the SLC44 family). Acetylcholine is accumulated in synaptic vesicles through the action of the vesicular acetylcholine transporter SLC18A3.

Nomenclature	choline O-acetyltransferase	acetylcholinesterase (Cartwright blood group)	butyrylcholinesterase
HGNC, UniProt	*CHAT*, P28329	*ACHE*, P22303	*BCHE*, P06276
EC number	2.3.1.6: acetyl CoA + choline = acetylcholine + coenzyme A	3.1.1.7: acetylcholine + H_2O = acetic acid + choline + H^+	3.1.1.7: acetylcholine + H_2O = acetic acid + choline + H^+
Common abreviation	ChAT	AChE	BChE
Inhibitors	compound 2 (pIC_{50} 6.5) [190] – Mouse	tacrine (pK_i 7.5) [58], galantamine (pIC_{50} 6.3) [94], rivastigmine (pIC_{50} 5.4) [325]	rivastigmine (pIC_{50} 7.4) [325], tacrine (pK_i 7.2) [58]
Sub/family-selective inhibitors	–	physostigmine (pIC_{50} 7.6–7.8) [325]	physostigmine (pIC_{50} 7.6–7.8) [325]
Selective inhibitors	–	donepezil (pIC_{50} 7.7–8.3) [68, 170, 325], BW284C51 (pIC_{50} 7.7) [182]	bambuterol (pIC_{50} 8.5) [182]
Comments	Splice variants of choline O-acetyltransferase are suggested to be differentially distributed in the periphery and CNS (see [30]).	–	–

Comments: A number of organophosphorus compounds inhibit acetylcholinesterase and cholinesterase irreversibly, including pesticides such as chlorpyrifos-oxon, and nerve agents such as tabun, soman and sarin. AChE is unusual in its exceptionally high turnover rate which has been calculated at 740 000/min/molecule [570].

Further reading on Acetylcholine turnover

Li Q *et al.* (2017) Recent progress in the identification of selective butyrylcholinesterase inhibitors for Alzheimer's disease. *Eur J Med Chem* **132**: 294-309 [PMID:28371641]

Lockridge O. (2015) Review of human butyrylcholinesterase structure, function, genetic variants, history of use in the clinic, and potential therapeutic uses. *Pharmacol Ther* **148**: 34-46 [PMID:25448037]

Masson P *et al.* (2016) Slow-binding inhibition of cholinesterases, pharmacological and toxicological relevance. *Arch Biochem Biophys* **593**: 60-8 [PMID:26874196]

Rotundo RL. (2017) Biogenesis, assembly and trafficking of acetylcholinesterase. *J Neurochem* [PMID:28326552]

Silman I *et al.* (2017) Recent developments in structural studies on acetylcholinesterase. *J Neurochem* [PMID:28503857]

Adenosine turnover

Enzymes → Adenosine turnover

Overview: A multifunctional, ubiquitous molecule, adenosine acts at cell-surface G protein-coupled receptors, as well as numerous enzymes, including protein kinases and adenylyl cyclase. Extracellular adenosine is thought to be produced either by export or by metabolism, predominantly through ecto-5′-nucleotidase activity (also producing inorganic phosphate). It is inactivated either by extracellular metabolism *via* adenosine deaminase (also producing ammonia) or, following uptake by nucleoside transporters, *via* adenosine deaminase or adenosine kinase (requiring ATP as co-substrate). Intracellular adenosine may be produced by cytosolic 5′-nucleotidases or through S-adenosylhomocysteine hydrolase (also producing L-homocysteine).

Nomenclature	Adenosine deaminase	Adenosine kinase	Ecto-5′-Nucleotidase	S-Adenosylhomocysteine hydrolase
Systematic nomenclature	–	–	CD73	–
HGNC, UniProt	*ADA*, P00813	*ADK*, P55263	*NT5E*, P21589	*AHCY*, P23526
EC number	3.5.4.4: adenosine + H_2O = inosine + NH_3	2.7.1.20	3.1.3.5	3.3.1.1
Common abreviation	ADA	ADK	NT5E	SAHH
Rank order of affinity	2′-deoxyadenosine > adenosine	adenosine	adenosine 5′-monophosphate, 5′-GMP, 5′-inosine monophosphate, 5′-UMP > 5′-dAMP, 5′-dGMP	–
Endogenous substrates	–	–	–	S-adenosylhomocysteine
Products	2′-deoxyinosine, inosine	adenosine 5′-monophosphate	uridine, inosine, guanine, adenosine	adenosine
Inhibitors	–	–	–	DZNep (pK_i 12.3) [184] – Hamster
Selective inhibitors	pentostatin (pIC_{50} 10.8) [4], EHNA (pK_i 8.8) [4]	A134974 (pIC_{50} 10.2) [348], ABT702 (pIC_{50} 8.8) [248]	αβ-methyleneADP (pIC_{50} 8.7) [56]	3-deazaadenosine (pIC_{50} 8.5) [197]
Comments	–	The enzyme exists in two isoforms derived from alternative splicing of a single gene product: a short isoform, ADK-S, located in the cytoplasm is responsible for the regulation of intra- and extracellular levels of adenosine and hence adenosine receptor activation; a long isoform, ADK-L, located in the nucleus contributes to the regulation of DNA methylation [48, 569].	Pharmacological inhibition of CD73 is being investigated as a novel cancer immunotherapy strategy [552].	–

Comments: An extracellular adenosine deaminase activity, termed ADA2 or adenosine deaminase growth factor (ADGF, *CECR1*, Q9NZK5) has been identified [101, 331], which is insensitive to EHNA [595]. Other forms of adenosine deaminase act on ribonucleic acids and may be divided into two families: *ADAT1* (Q9BUB4) deaminates transfer RNA; *ADAR* (EC 3.5.4.37, also known as 136 kDa double-stranded RNA-binding protein, P136, K88DSRBP, Interferon-inducible protein 4); *ADARB1* (EC 3.5.-.-, , also known as dsRNA adenosine deaminase) and *ADARB2* (EC 3.5.-.-, also known as dsRNA adenosine deaminase B2, RNA-dependent adenosine deaminase 3) act on double-stranded RNA. Particular polymorphisms of the ADA gene result in loss-of-function and severe combined immunodeficiency syndrome. Adenosine deaminase is able to complex with dipeptidyl peptidase IV (EC 3.4.14.5, *DPP4*, also known as T-cell activation antigen CD26, TP103, adenosine deaminase complexing protein 2) to form a cell-surface activity [259].

Further reading on Adenosine turnover

Boison D. (2013) Adenosine kinase: exploitation for therapeutic gain. *Pharmacol. Rev.* **65**: 906-43 [PMID:23592612]
Cortés A *et al.* (2015) Moonlighting adenosine deaminase: a target protein for drug development. *Med Res Rev* **35**: 85-125 [PMID:24933472]
Nishikura K (2016) A-to-I editing of coding and non-coding RNAs by ADARs. *Nat Rev Mol Cell Biol* **17**: 83-96 [PMID:26648264]
Sawynok J (2016) Adenosine receptor targets for pain. *Neuroscience* **338**: 1-18 [PMID:26500181]
Xiao Y *et al.* (2015) Role of S-adenosylhomocysteine in cardiovascular disease and its potential epigenetic mechanism. *Int J Biochem Cell Biol* **67**: 158-66 [PMID:26117455]

Amino acid hydroxylases

Enzymes → Amino acid hydroxylases

Overview: The amino acid hydroxylases (monooxygenases), EC.1.14.16.-, are iron-containing enzymes which utilise molecular oxygen and sapropterin as co-substrate and co-factor, respectively. In humans, as well as in other mammals, there are two distinct L-Tryptophan hydroxylase 2 genes. In humans, these genes are located on chromosomes 11 and 12 and encode two different homologous enzymes, TPH1 and TPH2.

Nomenclature	L-Phenylalanine hydroxylase	L-Tyrosine hydroxylase	L-Tryptophan hydroxylase 1	L-Tryptophan hydroxylase 2
HGNC, UniProt	*PAH*, P00439	*TH*, P07101	*TPH1*, P17752	*TPH2*, Q8IWU9
EC number	1.14.16.1: L-phenylalanine + O_2 -> L-tyrosine	1.14.16.2: L-tyrosine + O_2 -> levodopa	1.14.16.4	1.14.16.4
Endogenous substrates	L-phenylalanine	L-tyrosine	L-tryptophan	L-tryptophan
Products	L-tyrosine	levodopa	5-hydroxy-L-tryptophan	5-hydroxy-L-tryptophan
Cofactors	sapropterin	sapropterin, Fe^{2+}	–	–
Endogenous activators	Protein kinase A-mediated phosphorylation (Rat) [2]	Protein kinase A-mediated phosphorylation [251]	Protein kinase A-mediated phosphorylation [252]	Protein kinase A-mediated phosphorylation [252]
Inhibitors	–	methyltyrosine	telotristat ethyl [267]	–
Selective inhibitors	α-methylphenylalanine [191] – Rat, fenclonine	α-propyldopacetamide, 3-chlorotyrosine, 3-iodotyrosine, alpha-methyltyrosine	α-propyldopacetamide, 6-fluorotryptophan [377], fenclonine, fenfluramine	α-propyldopacetamide, 6-fluorotryptophan [377], fenclonine, fenfluramine

(continued)				
Nomenclature	L-Phenylalanine hydroxylase	L-Tyrosine hydroxylase	L-Tryptophan hydroxylase 1	L-Tryptophan hydroxylase 2
Comments	PAH is an iron bound homodimer or -tetramer from the same structural family as tyrosine 3-monooxygenase and the tryptophan hydroxylases. Deficiency or loss-of-function of PAH is associated with phenylketonuria	TH is a homotetramer, which is inhibited by dopamine and other catecholamines in a physiological negative feedback pathway [109].	–	–

Further reading on Amino acid hydroxylases

Bauer IE *et al.* (2015) Serotonergic gene variation in substance use pharmacotherapy: a systematic review. *Pharmacogenomics* **16**: 1307-14 [PMID:26265436]

Daubner SC *et al.* (2011) Tyrosine hydroxylase and regulation of dopamine synthesis. *Arch. Biochem. Biophys.* **508**: 1-12 [PMID:21176768]

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Roberts KM *et al.* (2013) Mechanisms of tryptophan and tyrosine hydroxylase. *IUBMB Life* **65**: 350-7 [PMID:23441081]

Tekin I *et al.* (2014) Complex molecular regulation of tyrosine hydroxylase. *J Neural Transm* **121**: 1451-81 [PMID:24866693]

Waloen K *et al.* (2017) Tyrosine and tryptophan hydroxylases as therapeutic targets in human disease. *Expert Opin Ther Targets* **21**: 167-180 [PMID:27973928]

L-Arginine turnover

Enzymes → L-Arginine turnover

Overview: L-arginine is a basic amino acid with a guanidino sidechain. As an amino acid, metabolism of L-arginine to form L-ornithine, catalysed by arginase, forms the last step of the urea production cycle. L-Ornithine may be utilised as a precursor of polyamines (see Carboxylases and Decarboxylases) or recycled via L-argininosuccinic acid to L-arginine. L-Arginine may itself be decarboxylated to form agmatine, although the prominence of this pathway in human tissues is uncertain. L-Arginine may be used as a precursor for guanidoacetic acid formation in the creatine synthesis pathway under the influence of arginine:glycine amidinotransferase with L-ornithine as a byproduct. Nitric oxide synthase uses L-arginine to generate nitric oxide, with L-citrulline also as a byproduct.
L-Arginine in proteins may be subject to post-translational modification through methylation, catalysed by protein arginine methyltransferases. Subsequent proteolysis can liberate asymmetric N^G,N^G-dimethyl-L-arginine (ADMA), which is an endogenous inhibitor of nitric oxide synthase activities. ADMA is hydrolysed by dimethylarginine dimethylhydrolase activities to generate L-citrulline and dimethylamine.

Further reading on L-Arginine turnover

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Pudlo M *et al.* (2017) Arginase Inhibitors: A Rational Approach Over One Century. *Med Res Rev* **37**: 475-513 [PMID:27862081]

Sudar-Milovanovic E *et al.* (2016) Benefits of L-Arginine on Cardiovascular. *System Mini Rev Med Chem* **16**: 94-103 [PMID:26471966]

2.1.1.- Protein arginine N-methyltransferases

Enzymes → L-Arginine turnover → 2.1.1.- Protein arginine N-methyltransferases

Overview: Protein arginine N-methyltransferases (PRMT, EC 2.1.1.-) encompass histone arginine *N*-methyltransferases (PRMT4, PRMT7, EC 2.1.1.125) and myelin basic protein *N*-methyltransferases (PRMT7, EC 2.1.1.126). They are dimeric or tetrameric enzymes which use S-adenosyl methionine as a methyl donor, generating S-adenosylhomocysteine as a by-product. They generate both mono-methylated and di-methylated products; these may be symmetric (SDMA) or asymmetric (N^G,N^G-dimethyl-L-arginine) versions, where both guanidine nitrogens are monomethylated or one of the two is dimethylated, respectively.

Information on members of this family may be found in the online database.

Arginase

Enzymes → L-Arginine turnover → Arginase

Overview: Arginase (EC 3.5.3.1) are manganese-containing isoforms, which appear to show differential distribution, where the ARG1 isoform predominates in the liver and erythrocytes, while ARG2 is associated more with the kidney.

Information on members of this family may be found in the online database.

Comments: N^{ω}-hydroxyarginine, an intermediate in NOS metabolism of L-arginine acts as a weak inhibitor and may function as a physiological regulator of arginase activity. Although isoform-selective inhibitors of arginase are not available, examples of inhibitors selective for arginase compared to NOS are N^{ω}-hydroxy-nor-L-arginine [525], S-(2-boronoethyl)-L-cysteine [97, 268] and 2(*S*)-amino-6-boronohexanoic acid [24, 97].

Arginine:glycine amidinotransferase

Enzymes → L-Arginine turnover → Arginine:glycine amidinotransferase

Nomenclature	Arginine:glycine amidinotransferase
HGNC, UniProt	*GATM*, P50440
EC number	2.1.4.1
Common abreviation	AGAT

Dimethylarginine dimethylaminohydrolases

Enzymes → L-Arginine turnover → Dimethylarginine dimethylaminohydrolases

Overview: Dimethylarginine dimethylaminohydrolases (DDAH, EC 3.5.3.18) are cytoplasmic enzymes which hydrolyse N^G,N^G-dimethyl-L-arginine to form dimethylamine and L-citrulline.

Nomenclature	N^G,N^G-Dimethylarginine dimethylaminohydrolase 1	N^G,N^G-Dimethylarginine dimethylaminohydrolase 2
HGNC, UniProt	*DDAH1*, O94760	*DDAH2*, O95865
EC number	3.5.3.18	3.5.3.18
Common abreviation	DDAH1	DDAH2
Cofactors	Zn^{2+}	–
Inhibitors	compound 2e (pK_i 5.7) [279]	–

Nitric oxide synthases

Enzymes → L-Arginine turnover → Nitric oxide synthases

Overview: Nitric oxide synthases (NOS, E.C. 1.14.13.39) are a family of oxidoreductases that synthesize nitric oxide (NO.) via the NADPH and oxygen-dependent consumption of L-arginine with the resultant by-product, L-citrulline. There are 3 NOS isoforms and they are related by their capacity to produce NO, highly conserved organization of functional domains and significant homology at the amino acid level. NOS isoforms are functionally distinguished by the cell type where they are expressed, intracellular targeting and transcriptional and post-translation mechanisms regulating enzyme activity. The nomenclature suggested by **NC-IUPHAR** of NOS I, II and III [363] has not gained wide acceptance, and the 3 isoforms are more commonly referred to as neuronal NOS (nNOS), inducible NOS (iNOS) and endothelial NOS (eNOS) which reflect the location of expression (nNOS and eNOS) and inducible expression (iNOS). All are dimeric enzymes that shuttle electrons from NADPH, which binds to a C-terminal reductase domain, through the flavins FAD and FMN to the oxygenase domain of the other monomer to enable the BH4-dependent reduction of heme bound oxygen for insertion into the substrate, L-arginine. Electron flow from reductase to oxygenase domain is controlled by calmodulin binding to canonical calmodulin binding motif located between these domains. eNOS and nNOS isoforms are activated at concentrations of calcium greater than 100 nM, while iNOS shows higher affinity for Ca^{2+}/calmodulin (*CALM1 CALM2 CALM3*, P62158) with great avidity and is essentially calcium-independent and constitutively active. Efficient stimulus-dependent coupling of nNOS and eNOS is achieved *via* subcellular targeting through respective N-terminal PDZ and fatty acid acylation domains whereas iNOS is largely cytosolic and function is independent of intracellular location. nNOS is primarily expressed in the brain and neuronal tissue, iNOS in immune cells such as macrophages and eNOS in the endothelial layer of the vasculature although exceptions in other cells have been documented. L-NAME and related modified arginine analogues are inhibitors of all three isoforms, with IC_{50} values in the micromolar range.

Nomenclature	Endothelial NOS	Inducible NOS	Neuronal NOS
HGNC, UniProt	*NOS3*, P29474	*NOS2*, P35228	*NOS1*, P29475
EC number	1.14.13.39	1.14.13.39	1.14.13.39
Common abreviation	eNOS	iNOS	nNOS
Endogenous Substrate	L-arginine	L-arginine	L-arginine
Products	NO, L-citrulline	NO, L-citrulline	L-citrulline, NO
Cofactors	oxygen, BH4, Zn^{2+}, flavin mononucleotide, NADPH, heme, flavin adenine dinucleotide	heme, flavin mononucleotide, flavin adenine dinucleotide, oxygen, NADPH, Zn^{2+}, BH4	flavin adenine dinucleotide, heme, oxygen, BH4, flavin mononucleotide, NADPH, Zn^{2+}
Selective inhibitors	–	1400W (pIC_{50} 8.2) [178], 2-amino-4-methylpyridine (pIC_{50} 7.4) [139], PIBTU (pIC_{50} 7.3) [179], NIL (pIC_{50} 5.5) [364], aminoguanidine [99]	3-bromo-7NI (pIC_{50} 6.1–6.5) [43], 7NI (pIC_{50} 5.3) [20]

Comments: The reductase domain of NOS catalyses the reduction of cytochrome c and other redox-active dyes [345]. NADPH:O_2 oxidoreductase catalyses the formation of superoxide anion/H_2O_2 in the absence of L-arginine and sapropterin.

Further reading on Nitric oxide synthases

Bogdan, C. (2015) Nitric oxide synthase in innate and adaptive immunity: An update. *Trends Immunol* **36**: 161-78 [PMID:25687683]

Lundberg JO *et al.* (2015) Strategies to increase nitric oxide signalling in cardiovascular disease. *Nat Rev Drug Discov* **14**: 623-41 [PMID:26265312]

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Shu X *et al.* (2015) Endothelial nitric oxide synthase in the microcirculation. *Cell Mol Life Sci* **72**: 4561-75 [PMID:26390975]

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Carboxylases and decarboxylases

Enzymes → Carboxylases and decarboxylases

Carboxylases

Enzymes → Carboxylases and decarboxylases → Carboxylases

Overview: The carboxylases allow the production of new carbon-carbon bonds by introducing HCO_3^- or CO_2 into target molecules. Two groups of carboxylase activities, some of which are bidirectional, can be defined on the basis of the cofactor requirement, making use of biotin (EC 6.4.1.-) or vitamin K hydroquinone (EC 4.1.1.-).

Nomenclature	Pyruvate carboxylase	Acetyl-CoA carboxylase 1	Acetyl-CoA carboxylase 2	Propionyl-CoA carboxylase	γ-Glutamyl carboxylase
HGNC, UniProt	*PC*, P11498	*ACACA*, Q13085	*ACACB*, O00763	–	*GGCX*, P38435
Subunits	–	–	–	Propionyl-CoA carboxylaseβ subunit, Propionyl-CoA carboxylase α subunit	–
EC number	6.4.1.1	6.4.1.2	6.4.1.2	6.4.1.3	4.1.1.90
Common abreviation	PC	ACC1	ACC2	PCCA,PCCB	GGCX
Endogenous substrates	ATP, pyruvic acid	ATP, acetyl CoA	acetyl CoA, ATP	propionyl-CoA, ATP	glutamyl peptides
Products	P_i, ADP, oxalacetic acid	P_i, ADP, malonyl-CoA	P_i, ADP, malonyl-CoA	ADP, methylmalonyl-CoA, P_i	carboxyglutamyl peptides
Cofactors	biotin	biotin	biotin	biotin	vitamin K hydroquinone, NADPH
Inhibitors	–	–	–	–	anisindione
Selective inhibitors	–	TOFA (pIC_{50} 4.9) [599]	TOFA (pIC_{50} 4.9) [599]	–	–
Comments	–	Citrate and other dicarboxylic acids are allosteric activators of acetyl-CoA carboxylase.		Propionyl-CoA carboxylase is able to function in both forward and reverse activity modes, as a ligase (carboxylase) or lyase (decarboxylase), respectively.	Loss-of-function mutations in γ-glutamyl carboxylase are associated with clotting disorders.

Comments: Dicarboxylic acids including citric acid are able to activate ACC1/ACC2 activity allosterically. PCC is able to function in forward and reverse modes as a ligase (carboxylase) or lyase (decarboxylase) activity, respectively. Loss-of-function mutations in GGCX are associated with clotting disorders.

Decarboxylases

Enzymes → Carboxylases and decarboxylases → Decarboxylases

Overview: The decarboxylases generate CO_2 and the indicated products from acidic substrates, requiring pyridoxal phosphate or pyruvic acid as a co-factor.

Nomenclature	Glutamic acid decarboxylase 1	Glutamic acid decarboxylase 2	Histidine decarboxylase
HGNC, UniProt	*GAD1*, Q99259	*GAD2*, Q05329	*HDC*, P19113
EC number	4.1.1.15: L-glutamic acid + H^+ -> GABA + CO_2	4.1.1.15: L-glutamic acid + H^+ -> GABA + CO_2	4.1.1.22
Common abreviation	GAD1	GAD2	HDC
Endogenous substrates	L-glutamic acid, L-aspartic acid	L-glutamic acid, L-aspartic acid	L-histidine
Products	GABA	GABA	histamine
Cofactors	pyridoxal phosphate	pyridoxal phosphate	pyridoxal phosphate
Selective inhibitors	s-allylglycine	s-allylglycine	AMA, FMH [174]
Comments	L-aspartic acid is a less rapidly metabolised substrate of mouse brain glutamic acid decarboxylase generating β-alanine [577]. Autoantibodies against GAD1 and GAD2 are elevated in type 1 diabetes mellitus and neurological disorders (see Further reading).		–

Nomenclature	L-Arginine decarboxylase	L-Aromatic amino-acid decarboxylase	Malonyl-CoA decarboxylase	Ornithine decarboxylase	Phosphatidylserine decarboxylase	S-Adenosylmethionine decarboxylase
HGNC, UniProt	*AZIN2*, Q96A70	*DDC*, P20711	*MLYCD*, O95822	*ODC1*, P11926	*PISD*, Q9UG56	*AMD1*, P17707
EC number	4.1.1.19	4.1.1.28: levodopa -> dopamine + CO_2 5-hydroxy-L-tryptophan -> 5-hydroxytryptamine + CO_2 This enzyme also catalyses the following reaction:: L-tryptophan -> tryptamine + CO_2	4.1.1.9	4.1.1.17	4.1.1.65	4.1.1.50
Common abreviation	ADC	AADC	MLYCD	ODC	PSDC	SAMDC

(continued)

Nomenclature	L-Arginine decarboxylase	L-Aromatic amino-acid decarboxylase	Malonyl-CoA decarboxylase	Ornithine decarboxylase	Phosphatidylserine decarboxylase	S-Adenosylmethionine decarboxylase
Endogenous substrates	L-arginine	levodopa, 5-hydroxy-L-tryptophan, L-tryptophan	malonyl-CoA	L-ornithine	phosphatidylserine	S-adenosyl methionine
Products	agmatine [601]	5-hydroxytryptamine, dopamine	acetyl CoA	putrescine	phosphatidylethanolamine	S-adenosyl-L-methioninamine
Cofactors	pyridoxal phosphate	pyridoxal phosphate	pyridoxal phosphate	pyridoxal phosphate	pyruvic acid	pyruvic acid
Selective inhibitors	–	3-hydroxybenzylhydrazine, L-α-methyldopa, benserazide [108], carbidopa	–	APA (pIC_{50} 7.5) [494], eflornithine (pK_d 4.9) [422]	–	sardomozide (pIC_{50} 8) [493]
Comments	The presence of a functional ADC activity in human tissues has been questioned [96].	AADC is a homodimer.	Inhibited by AMP-activated protein kinase-evoked phosphorylation [451]	The activity of ODC is regulated by the presence of an antizyme (ENSG00000104904) and an ODC antizyme inhibitor (ENSG00000155096).	S-allylglycine is also an inhibitor of SAMDC [393].	s-allylglycine is also an inhibitor of SAMDC [393].

Further reading on Carboxylases and decarboxylases

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Jitrapakdee S *et al.* (2008) Structure, mechanism and regulation of pyruvate carboxylase. *Biochem. J.* **413**: 369-87 [PMID:18613815]

Lietzan AD *et al.* (2014) Functionally diverse biotin-dependent enzymes with oxaloacetate decarboxylase activity. *Arch. Biochem. Biophys.* **544**: 75-86 [PMID:24184447]

Moya-García AA *et al.* (2009) Structural features of mammalian histidine decarboxylase reveal the basis for specific inhibition. *Br. J. Pharmacol.* **157**: 4-13 [PMID:19413567]

Tong L. (2013) Structure and function of biotin-dependent carboxylases. *Cell. Mol. Life Sci.* **70**: 863-91 [PMID:22869039]

Vance JE *et al.* (2013) Formation and function of phosphatidylserine and phosphatidylethanolamine in mammalian cells. *Biochim. Biophys. Acta* **1831**: 543-54 [PMID:22960354]

Catecholamine turnover

Enzymes → Catecholamine turnover

Overview: Catecholamines are defined by the presence of two adjacent hydroxyls on a benzene ring with a sidechain containing an amine. The predominant catacholamines in mammalian biology are the neurotransmitter/hormones dopamine, (-)-noradrenaline (norepinephrine) and (-)-adrenaline (epinephrine). These hormone/transmitters are synthesized by sequential metabolism from L-phenylalanine via L-tyrosine. Hydroxylation of L-tyrosine generates levodopa, which is decarboxylated to form dopamine. Hydroxylation of the ethylamine sidechain generates (-)-noradrenaline (norepinephrine), which can be methylated to form (-)-adrenaline (epinephrine). In particular neuronal and adrenal chromaffin cells, the catecholamines dopamine, (-)-noradrenaline and (-)-adrenaline are accumulated into vesicles under the influence of the vesicular monoamine transporters (VMAT1/SLC18A1 and VMAT2/SLC18A2). After release into the synapse or the bloodstream, catecholamines are accumulated through the action cell-surface transporters, primarily the dopamine (DAT/SLC6A3) and norepinephrine transporter (NET/SLC6A2). The primary routes of metabolism of these catecholamines are oxidation via monoamine oxidase activities of methylation via catechol O-methyltransferase.

Nomenclature	L-Phenylalanine hydroxylase	Tyrosine aminotransferase	L-Tyrosine hydroxylase	Dopamine beta-hydroxylase (dopamine beta-monooxygenase)	L-Aromatic amino-acid decarboxylase
HGNC, UniProt	*PAH*, P00439	*TAT*, P17735	*TH*, P07101	*DBH*, P09172	*DDC*, P20711
EC number	1.14.16.1: L-phenylalanine + O_2 -> L-tyrosine	2.6.1.5: L-tyrosine + α-ketoglutaric acid -> 4-hydroxyphenylpyruvic acid + L-glutamic acid	1.14.16.2: L-tyrosine + O_2 -> levodopa	1.14.17.1: dopamine + O_2 = (-)-noradrenaline + H_2O	4.1.1.28: levodopa -> dopamine + CO_2 5-hydroxy-L-tryptophan -> 5-hydroxytryptamine + CO_2 This enzyme also catalyses the following reaction:: L-tryptophan -> tryptamine + CO_2
Common abreviation	–	TAT	–	DBH	AADC
Endogenous substrates	L-phenylalanine	–	L-tyrosine	–	levodopa, 5-hydroxy-L-tryptophan, L-tryptophan
Products	L-tyrosine	–	levodopa	–	5-hydroxytryptamine, dopamine
Cofactors	sapropterin	pyridoxal phosphate	sapropterin, Fe^{2+}	Cu^{2+}, L-ascorbic acid	pyridoxal phosphate
Endogenous activators	Protein kinase A-mediated phosphorylation (Rat) [2]	–	Protein kinase A-mediated phosphorylation [251]	–	–

(continued)

Nomenclature	L-Phenylalanine hydroxylase	Tyrosine aminotransferase	L-Tyrosine hydroxylase	Dopamine beta-hydroxylase (dopamine beta-monooxygenase)	L-Aromatic amino-acid decarboxylase
Selective inhibitors	α-methylphenylalanine [191] – Rat, fenclonine	–	α-propyldopacetamide, 3-chlorotyrosine, 3-iodotyrosine, alpha-methyltyrosine	nepicastat (pIC_{50} 8) [496]	3-hydroxybenzylhydrazine, L-α-methyldopa, benserazide [108], carbidopa
Comments	PAH is an iron bound homodimer or -tetramer from the same structural family as tyrosine 3-monooxygenase and the tryptophan hydroxylases. Deficiency or loss-of-function of PAH is associated with phenylketonuria	Tyrosine may also be metabolized in the liver by tyrosine transaminase to generate 4-hydroxyphenylpyruvic acid, which can be further metabolized to homogentisic acid. TAT is a homodimer, where loss-of-function mutations are associated with type II tyrosinemia.	TH is a homotetramer, which is inhibited by dopamine and other catecholamines in a physiological negative feedback pathway [109].	DBH is a homotetramer. A protein structurally-related to DBH (*MOXD1*, Q6UVY6) has been described and for which a function has yet to be identified [76].	AADC is a homodimer.

Nomenclature	Phenylethanolamine N-methyltransferase	Monoamine oxidase A	Monoamine oxidase B	Catechol-O-methyltransferase
HGNC, UniProt	*PNMT*, P11086	*MAOA*, P21397	*MAOB*, P27338	*COMT*, P21964
EC number	2.1.1.28: (-)-noradrenaline -> (-)-adrenaline	1.4.3.4 (-)-adrenaline -> 3,4-dihydroxymandelic acid + NH_3 (-)-noradrenaline -> 3,4-dihydroxymandelic acid + NH_3tyramine -> 4-hydroxyphenyl acetaldehyde + NH_3 dopamine -> 3,4-dihydroxyphenylacetaldehyde + NH_3 5-hydroxytryptamine -> 5-hydroxyindole acetaldehyde + NH_3	1.4.3.4	2.1.1.6: S-adenosyl-L-methionine + a catechol = S-adenosyl-L-homocysteine + a guaiacol (-)-noradrenaline -> normetanephrine dopamine -> 3-methoxytyramine 3,4-dihydroxymandelic acid -> vanillylmandelic acid (-)-adrenaline -> metanephrine
Common abreviation	PNMT	MAO-A	MAO-B	COMT
Cofactors	S-adenosyl methionine	flavin adenine dinucleotide	flavin adenine dinucleotide	S-adenosyl methionine

(continued)

Nomenclature	Phenylethanolamine N-methyltransferase	Monoamine oxidase A	Monoamine oxidase B	Catechol-O-methyltransferase
Inhibitors	LY134046 (pK_i 7.6) [163]	moclobemide (pK_i 8.3) [247], phenelzine (Irreversible inhibition) (pK_i 7.3) [39], tranylcypromine (pIC_{50} 4.7) [587], selegiline (pK_i 4.2) [357], befloxatone [107], clorgiline, pirlindole [350]	rasagiline (pIC_{50} 7.8) [591], phenelzine (Irreversible inhibition) (pK_i 7.8) [39], lazabemide (pK_i 7.1) [200, 532], selegiline (pK_i 5.7–6) [121, 357], tranylcypromine (pIC_{50} 4.7) [587]	tolcapone (soluble enzyme) (pK_i 9.6) [317], tolcapone (membrane-bound enzyme) (pK_i 9.5) [317], entacapone (soluble enzyme) (pK_i 9.5) [317], entacapone (membrane-bound enzyme) (pK_i 8.7) [317]
Selective inhibitors	–	–	safinamide (pK_i 6.3) [38]	–
Comments	–	–	–	COMT appears to exist in both membrane-bound and soluble forms. COMT has also been described to methylate steroids, particularly hydroxyestradiols

Further reading on Catecholamine turnover

Dauvilliers Y *et al.* (2015) Catechol-O-methyltransferase, dopamine, and sleep-wake regulation. *Sleep Med Rev* **22**: 47-53 [PMID:25466290]
Deshwal S *et al.* (2017) Emerging role of monoamine oxidase as a therapeutic target for cardiovascular disease. *Curr Opin Pharmacol* **33**: 64-69 [PMID:28528298]
Fisar Z. (2016) Drugs related to monoamine oxidase activity. *Prog Neuropsychopharmacol Biol Psychiatry* **69**: 112-24 [PMID:26944656]
Ramsay RR. (2016). Molecular aspects of monoamine oxidase B. *Prog Neuropsychopharmacol Biol Psychiatry* **69**: 81-9 [PMID:26891670]
Waloen K *et al.* (2017). Tyrosine and tryptophan hydroxylases as therapeutic targets in human disease. *Expert Opin Ther Targets* **21**: 167-180 [PMID:27973928]

Ceramide turnover

Enzymes → Ceramide turnover

Overview: Ceramides are a family of sphingophospholipids synthesized in the endoplasmic reticulum, which mediate cell stress responses, including apoptosis, autophagy and senescence, Serine palmitoyltransferase generates 3-ketosphinganine, which is reduced to sphinganine (dihydrosphingosine). N-Acylation allows the formation of dihydroceramides, which are subsequently reduced to form ceramides. Once synthesized, ceramides are trafficked from the ER to the Golgi bound to the ceramide transfer protein, CERT (*COL4A3BP*, Q9Y5P4). Ceramide can be metabolized via multiple routes, ensuring tight regulation of its cellular levels. Addition of phosphocholine generates sphingomyelin while carbohydrate is added to form glucosyl- or galactosylceramides. Ceramidase re-forms sphingosine or sphinganine from ceramide or dihydroceramide. Phosphorylation of ceramide generates ceramide phosphate. The determination of accurate kinetic parameters for many of the enzymes in the sphingolipid metabolic pathway is complicated by the lipophilic nature of the substrates.

Serine palmitoyltransferase

Enzymes → Ceramide turnover → Serine palmitoyltransferase

Overview: The functional enzyme is a heterodimer of SPT1 (LCB1) with either SPT2 (LCB2) or SPT3 (LCB2B); the small subunits of SPT (ssSPTa or ssSPTb) bind to the heterodimer to enhance enzymatic activity. The complexes of SPT1/SPT2/ssSPTa and SPT1/SPT2/ssSPTb were most active with palmitoylCoA as substrate, with the latter complex also showing some activity with stearoylCoA [202]. Complexes involving SPT3 appeared more broad in substrate selectivity, with incorporation of myristoylCoA prominent for SPT1/SPT3/ssSPTa complexes, while SP1/SPT3/ssSPTb complexes had similar activity with C16, C18 and C20 acylCoAs [202].

Nomenclature	serine palmitoyltransferase long chain base subunit 1	serine palmitoyltransferase long chain base subunit 2	serine palmitoyltransferase long chain base subunit 3	serine palmitoyltransferase small subunit A	serine palmitoyltransferase small subunit B
HGNC, UniProt	*SPTLC1*, O15269	*SPTLC2*, O15270	*SPTLC3*, Q9NUV7	*SPTSSA*, Q969W0	*SPTSSB*, Q8NFR3
EC number	2.3.1.50: L-serine + palmitoyl-CoA -> 3-ketosphinganine + coenzyme A + CO_2	2.3.1.50: L-serine + palmitoyl-CoA -> 3-ketosphinganine + coenzyme A + CO_2	2.3.1.50: L-serine + palmitoyl-CoA -> 3-ketosphinganine + coenzyme A + CO_2	–	–
Common abreviation	SPT1	SPT2	SPT3	SPTSSA	SPTSSB
Cofactors	pyridoxal phosphate	pyridoxal phosphate	pyridoxal phosphate	–	–
Selective inhibitors	myriocin (pK_i 9.6) [358] – Mouse	myriocin [358]	myriocin [358]	–	–

Ceramide synthase

Enzymes → Ceramide turnover → Ceramide synthase

Overview: This family of enzymes, also known as sphingosine *N*-acyltransferase, is located in the ER facing the cytosol with an as-yet undefined topology and stoichiometry. Ceramide synthase *in vitro* is sensitive to inhibition by the fungal derived toxin, fumonisin B1.

Nomenclature	ceramide synthase 1	ceramide synthase 2	ceramide synthase 3	ceramide synthase 4	ceramide synthase 5	ceramide synthase 6
HGNC, UniProt	*CERS1*, P27544	*CERS2*, Q96G23	*CERS3*, Q8IU89	*CERS4*, Q9HA82	*CERS5*, Q8N5B7	*CERS6*, Q6ZMG9
EC number	2.3.1.24: acylCoA + sphinganine -> dihydroceramide + coenzyme A sphingosine + acylCoA -> ceramide + coenzyme A					
Common abreviation	CERS1	CERS2	CERS3	CERS4	CERS5	CERS6
Substrates	C18-CoA [543]	C24- and C26-CoA [292]	C26-CoA and longer [361, 424]	C18-, C20- and C22-CoA [438]	C16-CoA [288, 438]	C14- and C16-CoA [360]

Sphingolipid Δ^4-desaturase

Enzymes → Ceramide turnover → Sphingolipid Δ^4-desaturase

Overview: DEGS1 and DEGS2 are 4TM proteins.

Nomenclature	delta 4-desaturase, sphingolipid 1	delta 4-desaturase, sphingolipid 2
HGNC, UniProt	*DEGS1*, O15121	*DEGS2*, Q6QHC5
EC number	1.14.-.-	1.14.-.-
Cofactors	NAD	NAD
Inhibitors	RBM2-1B (pIC_{50} 4.7) [63]	–
Comments	Myristoylation of DEGS1 enhances its activity and targets it to the mitochondria [28].	–

Comments: DEGS1 activity is inhibited by a number of natural products, including curcumin and Δ^9-tetrahydrocannabinol [138].

Sphingomyelin synthase

Enzymes → Ceramide turnover → Sphingomyelin synthase

Overview: Following translocation from the ER to the Golgi under the influence of the ceramide transfer protein, sphingomyelin synthases allow the formation of sphingomyelin by the transfer of phosphocholine from the phospholipid phosphatidylcholine.
Sphingomyelin synthase-related protein 1 is structurally related but lacks sphingomyelin synthase activity.

Nomenclature	sphingomyelin synthase 1	sphingomyelin synthase 2	sterile alpha motif domain containing 8
HGNC, UniProt	*SGMS1*, Q86VZ5	*SGMS2*, Q8NHU3	*SAMD8*, Q96LT4
EC number	2.7.8.27: ceramide + phosphatidylcholine -> sphingomyelin + diacylglycerol	2.7.8.27: ceramide + phosphatidylcholine -> sphingomyelin + diacylglycerol	2.7.8.-: ceramide + phosphatidylethanolamine -> ceramide phosphoethanolamine
Inhibitors	compound 1j (pIC_{50} 5.7) [301]	compound D24 (pIC_{50} 4.9) [116]	–
Comments	–	Palmitoylation of sphingomyelin synthase 2 may allow targeting to the plasma membrane [517].	–

Sphingomyelin phosphodiesterase

Enzymes → Ceramide turnover → Sphingomyelin phosphodiesterase

Overview: Also known as sphingomyelinase.

Nomenclature	sphingomyelin phosphodiesterase 1	sphingomyelin phosphodiesterase 2	sphingomyelin phosphodiesterase 3	sphingomyelin phosphodiesterase 4	sphingomyelin phosphodiesterase acid-like 3A	sphingomyelin phosphodiesterase acid-like 3B
HGNC, UniProt	*SMPD1*, P17405	*SMPD2*, O60906	*SMPD3*, Q9NY59	*SMPD4*, Q9NXE4	*SMPDL3A*, Q92484	*SMPDL3B*, Q92485
EC number		3.1.4.12: sphingomyelin -> ceramide + phosphocholine			3.1.4.-: sphingomyelin -> ceramide + phosphocholine	
Inhibitors	–	inhibitor A (pK_i 5.8) [586] – Bovine	–	–	–	–

Neutral sphingomyelinase coupling factors

Enzymes → Ceramide turnover → Neutral sphingomyelinase coupling factors

Overview: Protein FAN [3] and polycomb protein EED [410] allow coupling between TNF receptors and neutral sphingomyelinase phosphodiesterases.

Nomenclature	embryonic ectoderm development	neutral sphingomyelinase activation associated factor
HGNC, UniProt	*EED*, O75530	*NSMAF*, Q92636
Selective inhibitors	A-395 (Binding) (pK_i 9.4) [217]	–

Ceramide glucosyltransferase

Enzymes → Ceramide turnover → Ceramide glucosyltransferase

Nomenclature	UDP-glucose ceramide glucosyltransferase
HGNC, UniProt	*UGCG*, Q16739
EC number	2.4.1.80: UDP-glucose + ceramide = uridine diphosphate + glucosylceramide
Inhibitors	miglustat (pK_i 5.1) [63]
Comments	Glycoceramides are an extended family of sphingolipids, differing in the content and organization of the sugar moieties, as well as the acyl sidechains.

Acid ceramidase

Enzymes → Ceramide turnover → Acid ceramidase

Overview: The six human ceramidases may be divided on the basis of pH optimae into acid, neutral and alkaline ceramidases, which also differ in their subcellular location.

Nomenclature	N-acylsphingosine amidohydrolase 1
HGNC, UniProt	*ASAH1*, Q13510
EC number	3.5.1.23: ceramide -> sphingosine + a fatty acid
Comments	This lysosomal enzyme is proteolysed to form the mature protein made up of two chains from the same gene product [274].

Neutral ceramidases

Enzymes → Ceramide turnover → Neutral ceramidases

Overview: The six human ceramidases may be divided on the basis of pH optimae into acid, neutral and alkaline ceramidases, which also differ in their subcellular location.

Nomenclature	N-acylsphingosine amidohydrolase 2	N-acylsphingosine amidohydrolase 2B
HGNC, UniProt	*ASAH2*, Q9NR71	*ASAH2B*, P0C7U1
EC number	3.5.1.23: ceramide -> sphingosine + a fatty acid	–
Comments	The enzyme is associated with the plasma membrane [516].	–

Comments: ASAH2B appears to be an enzymatically inactive protein, which may result from gene duplication and truncation.

Alkaline ceramidases

Enzymes → Ceramide turnover → Alkaline ceramidases

Overview: The six human ceramidases may be divided on the basis of pH optimae into acid, neutral and alkaline ceramidases, which also differ in their subcellular location.

Nomenclature	alkaline ceramidase 1	alkaline ceramidase 2	alkaline ceramidase 3
HGNC, UniProt	*ACER1*, Q8TDN7	*ACER2*, Q5QJU3	*ACER3*, Q9NUN7
EC number	3.5.1.23: ceramide -> sphingosine + a fatty acid	3.5.1.23: ceramide -> sphingosine + a fatty acid	3.5.1.-
Comments	ACER1 is associated with the ER [505].	ACER2 is associated with the Golgi apparatus [582].	ACER3 is associated with the ER and Golgi apparatus [336].

Ceramide kinase

Enzymes → Ceramide turnover → Ceramide kinase

Nomenclature	ceramide kinase
HGNC, UniProt	*CERK*, Q8TCT0
EC number	2.7.1.138: ceramide + ATP -> ceramide 1-phosphate + ADP
Inhibitors	NVP 231 (pIC_{50} 7.9) [188]

Comments: A ceramide kinase-like protein has been identified in the human genome (*CERKL*, Q49MI3).

Further reading on Ceramide turnover

Aburasayn H *et al.* (2016) Targeting ceramide metabolism in obesity. *Am J Physiol Endocrinol Metab* **311**: E423-35 [PMID:27382035]

Adada M *et al.* (2016) Inhibitors of the sphingomyelin cycle: Sphingomyelin synthases and sphingomyelinases. *Chem Phys Lipids* **197**: 45-59 [PMID:26200918]

Casals N *et al.* (2016) Carnitine palmitoyltransferase 1C: From cognition to cancer. *Prog Lipid Res* **61**: 134-48 [PMID:26708865]

Casasampere M *et al.* (2016) Inhibitors of dihydroceramide desaturase 1: Therapeutic agents and pharmacological tools to decipher the role of dihydroceramides in cell biology. *Chem Phys Lipids* 197: 33-44 [PMID:26248324]

Fucho R *et al.* (2017) Ceramides and mitochondrial fatty acid oxidation in obesity. *FASEB J* **31**: 1263-1272 [PMID:28003342]

Hernandez-Corbacho MJ *et al.* (2017) Sphingolipids in mitochondria. *Biochim Biophys Acta* **1862**: 56-68 [PMID:27697478]

Ilan Y. (2016) Compounds of the sphingomyelin-ceramide-glycosphingolipid pathways as secondary messenger molecules: new targets for novel therapies for fatty liver disease and insulin resistance. *Am J Physiol Gastrointest Liver Physiol* **310**: G1102-17 [PMID:27173510]

Iqbal J *et al.* (2017) Sphingolipids and Lipoproteins in Health and Metabolic Disorders. *Trends Endocrinol Metab* **28**: 506-518 [PMID:28462811]

Kihara A. (2016) Synthesis and degradation pathways, functions, and pathology of ceramides and epidermal acylceramides. *Prog Lipid Res* **63**: 50-69 [PMID:27107674]

Petrache I *et al.* (2016) Ceramide Signaling and Metabolism in Pathophysiological States of the Lung. *Annu Rev Physiol* **78**: 463-80 [PMID:26667073]

Rodriguez-Cuenca S *et al.* (2017) Sphingolipids and glycerophospholipids - The "ying and yang" of lipotoxicity in metabolic diseases. *Prog Lipid Res* **66**: 14-29 [PMID:28104532]

Sasset L *et al.* (2016) Sphingolipid De Novo Biosynthesis: A Rheostat of Cardiovascular Homeostasis. *Trends Endocrinol Metab* **27**: 807-819 [PMID:27562337]

Vogt D *et al.* (2017) Therapeutic Strategies and Pharmacological Tools Influencing S1P Signaling and Metabolism. *Med Res Rev* **37**: 3-51 [PMID:27480072]

Wegner MS *et al.* (2016) The enigma of ceramide synthase regulation in mammalian cells. *Prog Lipid Res* **63**: 93-119 [PMID:27180613]

Chromatin modifying enzymes

Enzymes → Chromatin modifying enzymes

Overview: Chromatin modifying enzymes, and other chromatin-modifying proteins, fall into three broad categories: **writers**, **readers** and **erasers**. The function of these proteins is to dynamically maintain cell identity and regulate processes such as differentiation, development, proliferation and genome integrity *via* recognition of specific 'marks' (covalent post-translational modifications) on histone proteins and DNA [280]. In normal cells, tissues and organs, precise co-ordination of these proteins ensures expression of only those genes required to specify phenotype or which are required at specific times, for specific functions. Chromatin modifications allow DNA modifications not coded by the DNA sequence to be passed on through the genome and underlies heritable phenomena such as X chromosome inactivation, aging, heterochromatin formation, reprogramming, and gene silencing (epigenetic control).
To date at least eight distinct types of modifications are found on histones. These include small covalent modifications such as acetylation, methylation, and phosphorylation, the attachment of larger modifiers such as ubiquitination or sumoylation, and ADP ribosylation, proline isomerization and deimination. Chromatin modifications and the functions they regulate in cells are reviewed by Kouzarides (2007) [280].
Writer proteins include the histone methyltransferases, histone acetyltransferases, some kinases and ubiquitin ligases.
Readers include proteins which contain methyl-lysine-recognition motifs such as bromodomains, chromodomains, tudor domains, PHD zinc fingers, PWWP domains and MBT domains.
Erasers include the histone demethylases and histone deacetylases (HDACs and sirtuins).
Dysregulated epigenetic control can be associated with human diseases such as cancer [137], where a wide variety of cellular and protein abberations are known to perturb chromatin structure, gene transcription and ultimately cellular pathways [27, 477]. Due to the reversible nature of epigenetic modifications, chromatin regulators are very tractable targets for drug discovery and the development of novel therapeutics. Indeed, small molecule inhibitors of writers (*e.g.* azacitidine and decitabine target the DNA methyltransferases DNMT1 and DNMT3 for the treatment of myelodysplastic syndromes [175, 565]) and erasers (*e.g.* the HDAC inhibitors vorinostat, romidepsin and belinostat for the treatment of T-cell lymphomas [153, 265]) are already being used in the clinic. The search for the next generation of compounds with improved specificity against chromatin-associated proteins is an area of intense basic and clinical research [61]. Current progress in this field is reviewed by Simó-Riudalbas and Esteller (2015) [478].

2.1.1.- Protein arginine N-methyltransferases

Enzymes → Chromatin modifying enzymes → 2.1.1.- Protein arginine N-methyltransferases

Overview: Protein arginine N-methyltransferases (PRMT, EC 2.1.1.-) encompass histone arginine *N*-methyltransferases (PRMT4, PRMT7, EC 2.1.1.125) and myelin basic protein *N*-methyltransferases (PRMT7, EC 2.1.1.126). They are dimeric or tetrameric enzymes which use S-adenosyl methionine as a methyl donor, generating S-adenosylhomocysteine as a by-product. They generate both mono-methylated and di-methylated products; these may be symmetric (SDMA) or asymmetric (N^G,N^G-dimethyl-L-arginine) versions, where both guanidine nitrogens are monomethylated or one of the two is dimethylated, respectively.

Information on members of this family may be found in the online database.

3.5.1.- Histone deacetylases (HDACs)

Enzymes → Chromatin modifying enzymes → 3.5.1.- Histone deacetylases (HDACs)

Overview: Histone deacetylases act as erasers of epigenetic acetylation marks on lysine residues in histones. Removal of the acetyl groups facilitates tighter packing of chromatin (heterochromatin formation) leading to transcriptional repression.
The histone deacetylase family has been classified in to five subfamilies based on phylogenetic comparison with yeast homologues:
Class I contains HDACs 1, 2, 3 and 8
Class IIa contains HDACs 4, 5, 7 and 9
Class IIb contains HDACs 6 and 10
Class III contains the sirtuins (SIRT1-7)
Class IV contains only HDAC11.
Classes I, II and IV use Zn^+ as a co-factor, whereas catalysis by Class III enzymes requires NAD^+ as a co-factor, and members of this subfamily have ADP-ribosylase activity in addition to protein deacetylase function [456].
HDACs have more general protein deacetylase activity, being able to deacetylate lysine residues in non-histone proteins [90] such as microtubules [233], the hsp90 chaperone [281] and the tumour suppressor p53 [322].
Dysregulated HDAC activity has been identified in cancer cells and tumour tissues [305, 444], making HDACs attractive molecular targets in the search for novel mechanisms to treat cancer [567]. Several small molecule HDAC inhibitors are already approved for clinical use: romidepsin, belinostat, vorinostat, panobinostat, belinostat, valproic acid and tucidinostat. HDACs and HDAC inhibitors currently in development as potential anticancer therapeutics are reviewed by Simó-Riudalbas and Esteller (2015) [478].

Information on members of this family may be found in the online database.

Cyclic nucleotide turnover/signalling

Enzymes → Cyclic nucleotide turnover/signalling

Overview: Cyclic nucleotides are second messengers generated by cyclase enzymes from precursor triphosphates and hydrolysed by phosphodiesterases. The cellular actions of these cyclic nucleotides are mediated through activation of protein kinases (cAMP- and cGMP-dependent protein kinases), ion channels (cyclic nucleotide-gated, CNG, and hyperpolarization and cyclic nucleotide-gated, HCN) and guanine nucleotide exchange factors (GEFs, Epac).

Adenylyl cyclases (ACs)

Enzymes → Cyclic nucleotide turnover/signalling → Adenylyl cyclases (ACs)

Overview: Adenylyl cyclase, E.C. 4.6.1.1, converts ATP to cyclic AMP and pyrophosphate. Mammalian membrane-bound adenylyl cyclases are typically made up of two clusters of six TM domains separating two intracellular, overlapping catalytic domains that are the target for the nonselective activators forskolin, NKH477 (except AC9, [419]) and $G\alpha_s$ (the stimulatory G protein α subunit). Adenosine and its derivatives (*e.g.* 2′,5′-dideoxyadenosine), acting through the P-site, appear to be physiological inhibitors of adenylyl cyclase activity [527]. Three families of adenylyl cyclase are distinguishable: calmodulin (*CALM1 CALM2 CALM3*, P62158)-stimulated (AC1, AC3 and AC8), Ca^{2+}-inhibitable (AC5, AC6 and AC9) and Ca^{2+}-insensitive (AC2, AC4 and AC7) forms.

Nomenclature	adenylyl cyclase 1	adenylyl cyclase 2 (brain)	adenylyl cyclase 3	adenylyl cyclase 4
HGNC, UniProt	*ADCY1*, Q08828	*ADCY2*, Q08462	*ADCY3*, O60266	*ADCY4*, Q8NFM4
Common abreviation	AC1	AC2	AC3	AC4
Endogenous activators	calmodulin (*CALM1 CALM2 CALM3*, P62158), PKC-evoked phosphorylation [246, 515]	Gβγ, PKC-evoked phosphorylation [80, 326, 520]	calmodulin (*CALM1 CALM2 CALM3*, P62158), PKC-evoked phosphorylation [89, 246]	Gβγ [173]
Endogenous inhibitors	$G\alpha_i$, $G\alpha_o$, Gβγ [520, 521]	–	$G\alpha_i$, RGS2, CaM kinase II-evoked phosphorylation [479, 521, 562]	PKC-evoked phophorylation [603]

Nomenclature	adenylyl cyclase 5	adenylyl cyclase 6	adenylyl cyclase 7	adenylyl cyclase 8	adenylyl cyclase 9
HGNC, UniProt	*ADCY5*, O95622	*ADCY6*, O43306	*ADCY7*, P51828	*ADCY8*, P40145	*ADCY9*, O60503
Common abreviation	AC5	AC6	AC7	AC8	AC9
Endogenous activators	PKC-evoked phophorylation [262]	–	PKC-evoked phosphorylation [561]	Ca^{2+} [62]	–
Endogenous inhibitors	$G\alpha_i$, Ca^{2+}, PKA-evoked phosphorylation [240, 243, 521]	$G\alpha_i$, Ca^{2+}, PKA-evoked phosphorylation, PKC-evoked phosphorylation [83, 289, 521, 590]	–	–	Ca^{2+}/calcineurin [402]
Inhibitors	NKY80 (pIC_{50} 5.2) [52, 390]	NKY80 (pIC_{50} 4.8) [52]	–	–	–

Comments: Nitric oxide has been proposed to inhibit AC5 and AC6 selectively [223], although it is unclear whether this phenomenon is of physiological significance. A soluble adenylyl cyclase has been described (*ADCY10*, Q96PN6 [54]), unaffected by either Gα or Gβγ subunits, which has been suggested to be a cytoplasmic bicarbonate (pH-insensitive) sensor [82]. It can be inhibited selectively by KH7 (pIC_{50} 5.0-5.5) [221].

Further reading on Adenylyl cyclases

Dessauer CW *et al.* (2017) International Union of Basic and Clinical Pharmacology. CI. Structures and Small Molecule Modulators of Mammalian Adenylyl Cyclases. *Pharmacol Rev* **69**: 93-139 [PMID:28255005]

Halls ML *et al.* (2017) Adenylyl cyclase signalling complexes - Pharmacological challenges and opportunities. *Pharmacol Ther* **172**: 171-180 [PMID:28132906]

Wu L *et al.* (2016) Adenylate cyclase 3: a new target for anti-obesity drug development. *Obes Rev* **17**: 907-14 [PMID:27256589]

Exchange protein activated by cyclic AMP (EPACs)

Enzymes → Cyclic nucleotide turnover/signalling → Exchange protein activated by cyclic AMP (EPACs)

Overview: Epacs are members of a family of guanine nucleotide exchange factors (ENSFM00250000000899), which also includes *RapGEF5* (GFR, KIAA0277, MR-GEF, Q92565) and *RapGEFL1* (Link-GEFII, Q9UHV5). They are activated endogenously by cyclic AMP and with some pharmacological selectivity by 8-pCPT-2′-O-Me-cAMP [134]. Once activated, Epacs induce an enhanced activity of the monomeric G proteins, Rap1 and Rap2 by facilitating binding of guanosine-5′-triphosphate in place of guanosine 5′-diphosphate, leading to activation of phospholipase C [459].

Nomenclature	Rap guanine nucleotide exchange factor 3	Rap guanine nucleotide exchange factor 4
HGNC, UniProt	*RAPGEF3*, O95398	*RAPGEF4*, Q8WZA2
Common abreviation	Epac1	Epac2
Inhibitors	ESI-09 (pIC_{50} 5.5) [12]	HJC 0350 (pIC_{50} 6.5) [78], ESI-09 (pIC_{50} 4.4–5.2) [12, 79]

Further reading on Exchange protein activated by cyclic AMP (EPAC)

Fujita T *et al.* (2017) The role of Epac in the heart. *Cell Mol Life Sci* **74**: 591-606 [PMID:27549789]
Parnell E *et al.* (2015) The future of EPAC-targeted therapies: agonism versus antagonism. *Trends Pharmacol Sci* **36**: 203-14 [PMID:25744542]
Wang P *et al.* (2017) Exchange proteins directly activated by cAMP (EPACs): Emerging therapeutic targets. *Bioorg Med Chem Lett* **27**: 1633-1639 [PMID:28283242]

Nitric oxide (NO)-sensitive (soluble) guanylyl cyclase

Enzymes → Cyclic nucleotide turnover/signalling → Guanylyl cyclases (GCs) → Nitric oxide (NO)-sensitive (soluble) guanylyl cyclase

Overview: Nitric oxide (NO)-sensitive (soluble) guanylyl cyclase (GTP diphosphate-lyase (cyclising)), E.C. 4.6.1.2, is a heterodimer comprising a β_1 subunit and one of two alpha subunits (α_1, α_2) giving rise to two functionally indistinguishable isoforms, GC-1 ($\alpha_1\beta_1$) and GC-2 ($\alpha_2\beta_1$) [449, 593]. A haem group is associated with the β subunit and is the target for the endogenous ligand NO, and, potentially, carbon monoxide [159]. The enzyme converts guanosine-5′-triphosphate to the intracellular second messenger cyclic guanosine-3′,5′-monophosphate (cyclic GMP).

Nomenclature	Guanylyl cyclase, $\alpha_1\beta_1$	Guanylyl cyclase, $\alpha_2\beta_1$
Subunits	Guanylyl cyclase β_1 subunit, Guanylyl cyclase α_1 subunit	Guanylyl cyclase β_1 subunit, Guanylyl cyclase α_2 subunit
Common abreviation	GC-1	GC-2
Endogenous ligands	NO, CO	NO, CO
Selective activators	YC-1 [159, 272, 449], cinaciguat [apo-GC-1] [500], riociguat [498, 499]	YC-1 [272, 449], cinaciguat [apo-GC-2] [500], riociguat [500, 499]
Selective inhibitors	NS 2028 (pIC_{50} 8.1) [389] – Bovine, ODQ (pIC_{50} 7.5) [177]	ODQ

Subunits

Nomenclature	Guanylyl cyclase α_1 subunit	Guanylyl cyclase α_2 subunit	Guanylyl cyclase β_1 subunit	Guanylyl cyclase β_2 subunit
HGNC, UniProt	*GUCY1A3*, Q02108	*GUCY1A2*, P33402	*GUCY1B3*, Q02153	*GUCY1B2*, O75343

Comments: ODQ also shows activity at other haem-containing proteins [142], while YC-1 may also inhibit cGMP-hydrolysing phosphodiesterases [158, 169].

Further reading on Nitric oxide (NO)-sensitive (soluble) guanylyl cyclase

Papapetropoulos A *et al.* (2015) Extending the translational potential of targeting NO/cGMP-regulated pathways in the CVS. *Br J Pharmacol* **172**: 1397-414 [PMID:25302549]
Pechanova O *et al.* (2015) Cardiac NO signalling in the metabolic syndrome. *Br J Pharmacol* **172**: 1415-33 [PMID:25297560]
Vanhoutte PM *et al.* (2016) Thirty Years of Saying NO: Sources, Fate, Actions, and Misfortunes of the Endothelium-Derived Vasodilator Mediator. *Circ Res* **119**: 375-96 [PMID:27390338]
Yetik-Anacak G *et al.* (2015) Gas what: NO is not the only answer to sexual function. *Br J Pharmacol* **172**: 1434-54 [PMID:24661203]

Phosphodiesterases, 3′,5′-cyclic nucleotide (PDEs)

Enzymes → Cyclic nucleotide turnover/signalling → Phosphodiesterases, 3′,5′-cyclic nucleotide (PDEs)

Overview: 3′,5′-Cyclic nucleotide phosphodiesterases (PDEs, 3′,5′-cyclic-nucleotide 5′-nucleotidohydrolase), E.C. 3.1.4.17, catalyse the hydrolysis of a 3′,5′-cyclic nucleotide (usually cyclic AMP or cyclic GMP). Isobutylmethylxanthine is a nonselective inhibitor with an IC_{50} value in the millimolar range for all isoforms except PDE 8A, 8B and 9A. A 2′,3′-cyclic nucleotide 3′-phosphodiesterase (E.C. 3.1.4.37 CNPase) activity is associated with myelin formation in the development of the CNS.

Nomenclature	phosphodiesterase 1A	phosphodiesterase 1B	phosphodiesterase 1C
HGNC, UniProt	*PDE1A*, P54750	*PDE1B*, Q01064	*PDE1C*, Q14123
Common abreviation	PDE1A	PDE1B	PDE1C
Rank order of affinity	cyclic GMP > cyclic AMP	cyclic GMP > cyclic AMP	cyclic GMP = cyclic AMP
Endogenous activators	calmodulin (*CALM1 CALM2 CALM3*, P62158)	calmodulin (*CALM1 CALM2 CALM3*, P62158)	calmodulin (*CALM1 CALM2 CALM3*, P62158)
Inhibitors	crisaborole (pIC_{50} 5.2) [8]	–	–
Selective inhibitors	SCH51866 (pIC_{50} 7.2) [542], vinpocetine (pIC_{50} 5.1) [319]	SCH51866 (pIC_{50} 7.2) [542]	SCH51866 (pIC_{50} 7.2) [542], vinpocetine (pIC_{50} 4.3) [319]

Nomenclature	phosphodiesterase 2A	phosphodiesterase 3A	phosphodiesterase 3B
HGNC, UniProt	*PDE2A*, O00408	*PDE3A*, Q14432	*PDE3B*, Q13370
Common abreviation	PDE2A	PDE3A	PDE3B
Rank order of affinity	cyclic AMP ≫ cyclic GMP	–	–
Endogenous activators	cyclic GMP	–	–
Endogenous inhibitors	–	cyclic GMP	cyclic GMP
Inhibitors	milrinone (pIC_{50} <6.5) [504]	cilostazol (pIC_{50} 6.7) [504], inamrinone (pIC_{50} 4.8) [480]	–
Selective inhibitors	BAY607550 (pIC_{50} 8.3–8.8) [47], EHNA (pIC_{50} 5.3) [355]	cilostamide (pIC_{50} 7.5) [504], anagrelide (pIC_{50} 7.1–7.3) [257, 341, 349], milrinone (pIC_{50} 6.3–6.4) [131, 504]	cilostamide (pIC_{50} 7.3) [504], cilostazol (pIC_{50} 6.4) [504], milrinone (pIC_{50} 6) [504], inamrinone (pIC_{50} 4.5) [504]
Comments	EHNA is also an inhibitor of adenosine deaminase (E.C. 3.5.4.4).	–	–

Nomenclature	phosphodiesterase 4A	phosphodiesterase 4B	phosphodiesterase 4C	phosphodiesterase 4D	phosphodiesterase 5A
HGNC, UniProt	*PDE4A*, P27815	*PDE4B*, Q07343	*PDE4C*, Q08493	*PDE4D*, Q08499	*PDE5A*, O76074
Common abreviation	PDE4A	PDE4B	PDE4C	PDE4D	PDE5A
Rank order of affinity	cyclic AMP ≫ cyclic GMP	cyclic AMP ≫ cyclic GMP	cyclic AMP ≫ cyclic GMP	cyclic AMP ≫ cyclic GMP	cyclic GMP > cyclic AMP
Endogenous activators	–	–	–	PKA-mediated phosphorylation [229]	Protein kinase A, protein kinase G [100]
Inhibitors	ibudilast (pIC_{50} 7.3) [275], RS-25344 (pIC_{50} 7.2) [453]	roflumilast (pIC_{50} 9.4) [321], ibudilast (pIC_{50} 7.2) [275], RS-25344 (pIC_{50} 6.5) [453]	RS-25344 (pIC_{50} 8.1) [453], ibudilast (pIC_{50} 6.6) [275]	RS-25344 (pIC_{50} 8.4) [453]	gisadenafil (pIC_{50} 8.9) [433], milrinone (pIC_{50} 7.3)
Sub/family-selective inhibitors	rolipram (pIC_{50} 9) [553], CDP840 (pK_i 8) [406], Ro20-1724 (pIC_{50} 6.5) [553]	rolipram (pIC_{50} 9) [553], Ro20-1724 (pIC_{50} 6.4) [553]	CDP840 (pK_i 7.7) [406], rolipram (pIC_{50} 6.5) [553], Ro20-1724 (pIC_{50} 5.4) [553]	CDP840 (pK_i 8.1) [406], rolipram (pIC_{50} 7.2) [553], Ro20-1724 (pIC_{50} 6.2) [553]	–
Selective inhibitors	YM976 (pIC_{50} 8.3) [14], apremilast (pIC_{50} 7.8) [457]	–	apremilast (pIC_{50} 6.9) [457]	apremilast (pIC_{50} 7.5) [457]	vardenafil (pIC_{50} 9.7) [51], T0156 (pIC_{50} 9.5) [362], sildenafil (pIC_{50} 8.4–9) [538, 551], tadalafil (pIC_{50} 8.5) [379], SCH51866 (pIC_{50} 7.2) [542], zaprinast (pIC_{50} 6.8) [538]

Nomenclature	phosphodiesterase 6A	phosphodiesterase 6B	phosphodiesterase 6C	phosphodiesterase 6D	phosphodiesterase 6G	phosphodiesterase 6H
HGNC, UniProt	*PDE6A*, P16499	*PDE6B*, P35913	*PDE6C*, P51160	*PDE6D*, O43924	*PDE6G*, P18545	*PDE6H*, Q13956
Common abreviation	PDE6A	PDE6B	PDE6C	PDE6D	PDE6G	PDE6H
Inhibitors	–	–	sildenafil (pIC_{50} 7.4) [551]	–	–	–

Nomenclature	phosphodiesterase 7A	phosphodiesterase 7B	phosphodiesterase 8A	phosphodiesterase 8B
HGNC, UniProt	*PDE7A*, Q13946	*PDE7B*, Q9NP56	*PDE8A*, O60658	*PDE8B*, O95263
Common abreviation	PDE7A	PDE7B	PDE8A	PDE8B
Rank order of affinity	cyclic AMP ≫ cyclic GMP [353]	cyclic AMP ≫ cyclic GMP [176]	cyclic AMP ≫ cyclic GMP [146]	cyclic AMP ≫ cyclic GMP [214]
Inhibitors	crisaborole (pIC_{50} 6.1) [8]	BRL50481 (pIC_{50} 4.9) [9]	–	–
Selective inhibitors	BRL50481 (pIC_{50} 6.7–6.8) [9, 486]	dipyridamole (pIC_{50} 5.7–6) [179, 455], SCH51866 (pIC_{50} 5.8) [455]	dipyridamole (pIC_{50} 5.1) [146]	dipyridamole (pIC_{50} 4.3) [214]
Comments	PDE7A appears to be membrane-bound or soluble for PDE7A1 and 7A2 splice variants, respectively	–	–	–

Nomenclature	phosphodiesterase 9A	phosphodiesterase 10A	phosphodiesterase 11A
HGNC, UniProt	*PDE9A*, O76083	*PDE10A*, Q9Y233	*PDE11A*, Q9HCR9
Common abreviation	PDE9A	PDE10A	PDE11A
Rank order of affinity	cyclic GMP ≫ cyclic AMP [145]	cyclic AMP, cyclic GMP [161]	cyclic AMP, cyclic GMP [141]
Inhibitors	SCH51866 (pIC_{50} 5.8) [145], zaprinast (pIC_{50} 4.5) [145]	–	tadalafil (pIC_{50} 6.5) [379], BC11-38 (pIC_{50} 6.5) [79]

Comments: PDE1A, 1B and 1C appear to act as soluble homodimers, while PDE2A is a membrane-bound homodimer. PDE3A and PDE3B are membrane-bound.
PDE4 isoforms are essentially cyclic AMP specific. The potency of YM976 at other members of the PDE4 family has not been reported. PDE4B–D long forms are inhibited by extracellular signal-regulated kinase (ERK)-mediated phosphorylation [224, 225]. PDE4A–D splice variants can be membrane-bound or cytosolic [229]. PDE4 isoforms may be labelled with [^{3}H]rolipram.

PDE6 is a membrane-bound tetramer composed of two catalytic chains (PDE6A or PDE6C and PDE6B), an inhibitory chain (PDE6G or PDE6H) and the PDE6D chain. The enzyme is essentially cyclic GMP specific and is activated by the α-subunit of transducin ($G\alpha_t$) and inhibited by sildenafil, zaprinast and dipyridamole with potencies lower than those observed for PDE5A. Defects in PDE6B are a cause of retinitis pigmentosa and congenital stationary night blindness.

Further reading on Phosphodiesterases, 3',5'-cyclic nucleotide (PDEs)

Das A *et al.* (2015) PDE5 inhibitors as therapeutics for heart disease, diabetes and cancer. *Pharmacol Ther* **147**: 12-21 [PMID:25444755]

Jorgensen C *et al.* (2015) Phosphodiesterase4D (PDE4D)–A risk factor for atrial fibrillation and stroke? *J Neurol Sci* **359**: 266-74 [PMID:26671126]

Klussmann E. (2016) Protein-protein interactions of PDE4 family members - Functions, interactions and therapeutic value. *Cell Signal* **28**: 713-8 [PMID:26498857]

Korkmaz-Icoz S *et al.* (2017) Targeting phosphodiesterase 5 as a therapeutic option against myocardial ischaemia/reperfusion injury and for treating heart failure. *Br J Pharmacol* [PMID:28213937]

Leal LF *et al.* (2015) Phosphodiesterase 8B and cyclic AMP signaling in the adrenal cortex. *Endocrine* **50**: 27-31 [PMID:25971952]

Movsesian M. (2016) Novel approaches to targeting PDE3 in cardiovascular disease. *Pharmacol Ther* **163**: 74-81 [PMID:27108947]

Ricciarelli R *et al.* (2015) Phosphodiesterase 4D: an enzyme to remember. *Br J Pharmacol* **172**: 4785-9 [PMID:26211680]

Wu C *et al.* (2016) Phosphodiesterase-4 inhibition as a therapeutic strategy for metabolic disorders. *Obes Rev* **17**: 429-41 [PMID:26997580]

Cytochrome P450

Enzymes → Cytochrome P450

Overview: The cytochrome P450 enzyme family (CYP450), E.C. 1.14.-.-, were originally defined by their strong absorbance at 450 nm due to the reduced carbon monoxide-complexed haem component of the cytochromes. They are an extensive family of haem-containing monooxygenases with a huge range of both endogenous and exogenous substrates. Listed below are the human enzymes; their relationship with rodent CYP450 enzyme activities is obscure in that the species orthologue may not mediate metabolism of the same substrates. Although the majority of CYP450 enzyme activities are concentrated in the liver, the extrahepatic enzyme activities also contribute to patho/physiological processes. Genetic variation of CYP450 isoforms is widespread and likely underlies a significant proportion of the individual variation to drug administration.

CYP1 family

Enzymes → Cytochrome P450 → CYP1 family

Nomenclature	CYP1A1	CYP1A2	CYP1B1
HGNC, UniProt	*CYP1A1*, P04798	*CYP1A2*, P05177	*CYP1B1*, Q16678
EC number	1.14.1.1	1.14.1.1	1.14.1.1
Comments	–	–	Mutations have been associated with primary congenitial glucoma [503]

CYP2 family

Enzymes → Cytochrome P450 → CYP2 family

Nomenclature	CYP2A6	CYP2A7	CYP2C8	CYP2J2	CYP2R1
HGNC, UniProt	*CYP2A6*, P11509	*CYP2A7*, P20853	*CYP2C8*, P10632	*CYP2J2*, P51589	*CYP2R1*, Q6VVX0
EC number	1.14.14.1	1.14.14.1	1.14.14.1	1.14.14.1	1.14.13.15
Inhibitors	–	–	phenelzine (pK_i 5.1) [150]	terfenadine (pIC_{50} 5.1) [287]	–
Comments	Metabolises nicotine.	CYP2A7 does not incorporate haem and is functionally inactive [162]	Converts arachidonic acid to 11(R)-12(S)-epoxyeicosatrienoic acid or 14(R)-15(S)-epoxyeicosatrienoic acid [596].	Converts arachidonic acid to 14(R)-15(S)-epoxyeicosatrienoic acid [579].	Converts vitamin D3 to calcifediol [85].

CYP3 family

Enzymes → Cytochrome P450 → CYP3 family

Nomenclature	CYP3A4
HGNC, UniProt	*CYP3A4*, P08684
EC number	1.14.13.32: Albendazole + NADPH + O_2 = albendazole S-oxide + $NADP^+$ + H_2 1.14.13.157: 1,8-cineole + NADPH + O_2 = 2-exo-hydroxy-1,8-cineole + $NADP^+$ + H_2O 1.14.13.97: Taurochenodeoxycholate + NADPH + O_2 = taurohyocholate + $NADP^+$ + H_2O Lithocholate + NADPH + O_2 = hyodeoxycholate + $NADP^+$ + H_2O 1.14.13.67: quinine + NADPH + O_2 = 3-hydroxyquinine + $NADP^+$ + H_2O_2
Substrates	atorvastatin [155], codeine [155], diazepam [155], tamoxifen [155], erlotinib [155]
Products	4-hydroxy-tamoxifen quinone methide [469], 4-hydroxy-tamoxifen [469]
Inhibitors	ritonavir (pK_i >7) [266]
Comments	Metabolises a vast range of xenobiotics, including antidepressants, benzodiazepines, calcium channel blockers, and chemotherapeutic agents. CYP3A4 catalyses the 25-hydroxylation of trihydroxycholestane in liver microsomes [166].

CYP4 family

Enzymes → Cytochrome P450 → CYP4 family

Nomenclature	CYP4A11	CYP4F2	CYP4F3	CYP4F8
HGNC, UniProt	*CYP4A11*, Q02928	*CYP4F2*, P78329	*CYP4F3*, Q08477	*CYP4F8*, P98187
EC number	1.14.15.3	1.14.13.30	1.14.13.30	1.14.14.1
Inhibitors	–	17-octadecynoic acid (pK_i 5.9) [470]	–	–
Comments	Converts lauric acid to 12-hydroxylauric acid.	Responsible for ω-hydroxylation of LTB_4, LXB_4 [359], and tocopherols, including vitamin E [491]	Responsible for ω-hydroxylation of LTB_4, LXB_4 [359], and polyunsaturated fatty acids [143, 207]	Converts PGH_2 to 19-hydroxyPGH_2 [60] and 8,9-EET or 11,12-EET to 18-hydroxy-8,9-EET or 18-hydroxy-11,12-EET [378].

Nomenclature	CYP4F12	CYP4F22	CYP4V2	CYP4X1	CYP4Z1
HGNC, UniProt	*CYP4F12*, Q9HCS2	*CYP4F22*, Q6NT55	*CYP4V2*, Q6ZWL3	*CYP4X1*, Q8N118	*CYP4Z1*, Q86W10
EC number	1.14.14.1	1.14.14.-	1.14.-.-	1.14.14.1	1.14.14.1
Comments	AC004597.1 (ENSG00000225607) is described as being highly similar to CYP4F12	Converts arachidonic acid to 16-HETE and 18-HETE [378].	Converts myristic acid to 14-hydroxymyristic acid [372].	Converts anandamide to 14,15-epoxyeicosatrienoic ethanolamide [497].	Converts lauric acid to 12-hydroxylauric acid.

Comments: Converts lauric acid to 12-hydroxylauric acid.

CYP5, CYP7 and CYP8 families

Enzymes → Cytochrome P450 → CYP5, CYP7 and CYP8 families

Nomenclature	CYP5A1	CYP7A1	CYP7B1	CYP8A1	CYP8B1
HGNC, UniProt	*TBXAS1*, P24557	*CYP7A1*, P22680	*CYP7B1*, O75881	*PTGIS*, Q16647	*CYP8B1*, Q9UNU6
EC number	5.3.99.5: PGH_2 = thromboxane A_2	1.14.13.17	1.14.13.100	5.3.99.4	1.14.13.95
Common name	Thromboxane synthase	–	–	Prostacyclin synthase	–
Comments	Inhibited by dazoxiben [427] and camonagrel [194].	Converts cholesterol to 7α-hydroxycholesterol [379].	Converts dehydroepiandrosterone to 7α-DHEA [445].	Converts PGH_2 to PGI_2 [209]. Inhibited by tranylcypromine [193]	Converts 7α-hydroxycholest-4-en-3-one to 7-alpha,12α-dihydroxycholest-4-en-3-one (in rabbit) [239] in the biosynthesis of bile acids.

CYP11, CYP17, CYP19, CYP20 and CYP21 families

Enzymes → Cytochrome P450 → CYP11, CYP17, CYP19, CYP20 and CYP21 families

Nomenclature	CYP11A1	CYP11B1	CYP11B2
HGNC, UniProt	*CYP11A1*, P05108	*CYP11B1*, P15538	*CYP11B2*, P19099
EC number	1.14.15.6	1.14.15.4	1.14.15.4 1.14.15.5
Common name	–	–	Aldosterone synthase
Inhibitors	mitotane [297, 303]	metyrapone (pIC_{50} 7.8) [602], mitotane	osilodrostat (pIC_{50} 9.7) [585]
Comments	Converts cholesterol to pregnenolone plus 4-methylpentanal.	Converts deoxycortisone and 11-deoxycortisol to cortisone and cortisol, respectively. Loss-of-function mutations are associated with familial adrenal hyperplasia and hypertension. Inhibited by metyrapone [558]	Converts corticosterone to aldosterone

Nomenclature	CYP17A1	CYP19A1	CYP20A1	CYP21A2
HGNC, UniProt	*CYP17A1*, P05093	*CYP19A1*, P11511	*CYP20A1*, Q6UW02	*CYP21A2*, P08686
EC number	1.14.99.9	1.14.14.1	1.14.-.-	1.14.99.10
Common name	–	Aromatase	–	–
Inhibitors	abiraterone (pIC_{50} 7.1–8.4) [413, 417]	anastrozole (pIC_{50} 7.8) [367], aminoglutethimide [405]	–	(2S,4S)-ketoconazole (pIC_{50} 5.3) [447] – Rat
Selective inhibitors	galeterone (pIC_{50} 6.5) [204]	letrozole (pK_i 10.7) [346], exemestane (pIC_{50} 7.3) [92], testolactone (pK_i 4.5) [102]	–	–
Comments	Converts pregnenolone and progesterone to 17α-hydroxypregnenolone and 17α-hydroxyprogesterone, respectively. Converts 17α-hydroxypregnenolone and 17α-hydroxyprogesterone to dehydroepiandrosterone and androstenedione, respectively. Converts corticosterone to cortisol.	Converts androstenedione and testosterone to estrone and 17β-estradiol, respectively. Inhibited by anastrozole [415], and letrozole [35]	–	Converts progesterone and 17α-hydroxyprogesterone to deoxycortisone and 11-deoxycortisol, respectively

CYP24, CYP26 and CYP27 families

Enzymes → Cytochrome P450 → CYP24, CYP26 and CYP27 families

Nomenclature	CYP24A1	CYP26A1	CYP26B1	CYP27A1	CYP27B1
HGNC, UniProt	*CYP24A1*, Q07973	*CYP26A1*, O43174	*CYP26B1*, Q9NR63	*CYP27A1*, Q02318	*CYP27B1*, O15528
EC number	1.14.13.126	1.14.-.-	1.14.-.-	1.14.13.15	1.14.13.13
Common name	–	–	–	Sterol 27-hydroxylase	–
Comments	Converts 1,25-dihydroxyvitamin D3 (calcitriol) to 1α,24R,25-trihydroxyvitamin D_3.	Converts retinoic acid to 4-hydroxyretinoic acid. Inhibited by liarozole	Converts retinoic acid to 4-hydroxyretinoic acid.	Converts cholesterol to 27-hydroxycholesterol.	Converts 25-hydroxyvitamin D_3 to 1,25-dihydroxyvitamin D3 (calcitriol)

CYP39, CYP46 and CYP51 families

Enzymes → Cytochrome P450 → CYP39, CYP46 and CYP51 families

Nomenclature	CYP39A1	CYP46A1	CYP51A1
HGNC, UniProt	*CYP39A1*, Q9NYL5	*CYP46A1*, Q9Y6A2	*CYP51A1*, Q16850
EC number	1.14.13.99	1.14.13.98	–
Common name	–	Cholesterol 24-hydroxylase	Lanosterol 14-α-demethylase
Inhibitors	–	–	azalanstat (pK_i 9.1) [549]
Comments	Converts 24-hydroxycholesterol to 7α,24-dihydroxycholesterol [302].	Converts cholesterol to 24(S)-hydroxycholesterol.	Converts lanosterol to 4,4-dimethylcholesta-8.14.24-trienol.

Further reading on Cytochrome P450

Backman JT *et al.* (2016) Role of Cytochrome P450 2C8 in Drug Metabolism and Interactions. *Pharmacol Rev* **68**: 168-241 [PMID:26721703]

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Ghosh D *et al.* (2016) Recent Progress in the Discovery of Next Generation Inhibitors of Aromatase from the Structure-Function Perspective. *J Med Chem* **59**: 5131-48 [PMID:26689671]

Go RE *et al.* (2015) Cytochrome P450 1 family and cancers. *J Steroid Biochem Mol Biol* **147**: 24-30 [PMID:25448748]

Guengerich FP *et al.* (2016) Recent Structural Insights into Cytochrome P450 Function. *Trends Pharmacol Sci* **37**: 625-40 [PMID:27267697]

Isvoran A *et al.* (2017) Pharmacogenomics of the cytochrome P450 2C family: impacts of amino acid variations on drug metabolism. *Drug Discov Today* **22**: 366-376 [PMID:27693711]

Jamieson KL *et al.* (2017) Cytochrome P450-derived eicosanoids and heart function. *Pharmacol Ther* [PMID:28551025]

Mak PJ *et al.* (2017) Spectroscopic studies of the cytochrome P450 reaction mechanisms. *Biochim Biophys Acta* [PMID:28668640]

Moutinho M *et al.* (2016) Cholesterol 24-hydroxylase: Brain cholesterol metabolism and beyond. *Biochim Biophys Acta* **1861** 1911-1920 [PMID:27663182]

Shalan H *et al.* (2017) Keeping the spotlight on cytochrome P450. *Biochim Biophys Acta* [PMID:28599858]

Endocannabinoid turnover

Enzymes → Endocannabinoid turnover

Overview: The principle endocannabinoids are 2-acylglycerol esters, such as 2-arachidonoylglycerol (2AG), and *N*-acylethanolamines, such as anandamide (*N*-arachidonoylethanolamine, AEA). The glycerol esters and ethanolamides are synthesised and hydrolysed by parallel, independent pathways. Mechanisms for release and re-uptake of endocannabinoids (and related entities) are unclear, although candidates for intracellular transport have been suggested. For the generation of 2-arachidonoylglycerol, the key enzyme involved is diacylglycerol lipase (DGL), whilst several routes for anandamide synthesis have been described, the best characterized of which involves *N*-acylphosphatidylethanolamine-phospholipase D (NAPE-PLD, [476]). A transacylation enzyme which forms *N*-acylphosphatidylethanolamines has recently been identified as a cytosolic enzyme, *PLA2G4E* (Q3MJ16) [383]. *In vitro* experiments indicate that the endocannabinoids are also substrates for oxidative metabolism *via* cyclooxygenase, lipoxygenase and cytochrome P450 enzyme activities [11, 154, 488].

N-Acylethanolamine turnover

Enzymes → Endocannabinoid turnover → *N*-Acylethanolamine turnover

Nomenclature	*N*-Acylphosphatidylethanolamine-phospholipase D	Fatty acid amide hydrolase	Fatty acid amide hydrolase-2	*N*-Acylethanolamine acid amidase
HGNC, UniProt	*NAPEPLD*, Q6IQ20	*FAAH*, O00519	*FAAH2*, Q6GMR7	*NAAA*, Q02083
EC number	–	3.5.1.99: anandamide + H_2O <=> arachidonic acid + ethanolamine oleamide + H_2O <=> oleic acid + NH_3 The enzyme is responsible for the catabolism of neuromodulatory fatty acid amides, including anandamide and oleamide: anandamide + H_2O <=> arachidonic acid + ethanolamine oleamide + H_2O <=> oleic acid + NH_3	3.5.1.99: anandamide + H_2O <=> arachidonic acid + ethanolamine oleamide + H_2O <=> oleic acid + NH_3 The enzyme is responsible for the catabolism of neuromodulatory fatty acid amides, including anandamide and oleamide: anandamide + H_2O <=> arachidonic acid + ethanolamine oleamide + H_2O <=> oleic acid + NH_3	3.5.1.-
Common abreviation	NAPE-PLD	FAAH	FAAH2	NAAA
Rank order of affinity	–	anandamide > oleamide > N-oleoylethanolamide > N-palmitoylethanolamine [563]	oleamide > N-oleoylethanolamide > anandamide > N-palmitoylethanolamine [563]	N-palmitoylethanolamine > MEA > SEA ≥ N-oleoylethanolamide > anandamide [539]
Selective inhibitors	–	JNJ1661010 (pIC_{50} 7.8) [264], PF750 (pIC_{50} 6.3–7.8) [5], OL135 (pIC_{50} 7.4) [563], URB597 (pIC_{50} 6.3–7) [563], PF3845 (pIC_{50} 6.6) [6]	OL135 (pIC_{50} 7.9–8.4) [261, 563], URB597 (pIC_{50} 7.5–8.3) [261, 563]	*S*-OOPP (pIC_{50} 6.4) [489] – Rat, CCP (pIC_{50} 5.3) [535]

(continued)

Nomenclature	*N*-Acylphosphatidylethanolamine-phospholipase D	Fatty acid amide hydrolase	Fatty acid amide hydrolase-2	*N*-Acylethanolamine acid amidase
Comments	NAPE-PLD activity appears to be enhanced by polyamines in the physiological range [311], but fails to transphosphatidylate with alcohols [408] unlike phosphatidylcholine-specific phospholipase D.	–	The FAAH2 gene is found in many primate genomes, marsupials, and other distantly related vertebrates, but not a variety of lower placental mammals, including mouse and rat [563].	–

Comments: Routes for *N*-acylethanolamine biosynthesis other than through NAPE-PLD activity have been identified [536].

2-Acylglycerol ester turnover

Enzymes → Endocannabinoid turnover → 2-Acylglycerol ester turnover

Nomenclature	Diacylglycerol lipase α	Diacylglycerol lipase β	Monoacylglycerol lipase	αβ-Hydrolase 6
HGNC, UniProt	*DAGLA*, Q9Y4D2	*DAGLB*, Q8NCG7	*MGLL*, Q99685	*ABHD6*, Q9BV23
EC number	3.1.1.-	3.1.1.-	3.1.1.23	3.1.1.23
Common abreviation	DAGLα	DAGLβ	MAGL	ABHD6
Endogenous substrates	diacylglycerol	diacylglycerol	2-oleoyl glycerol = 2-arachidonoylglycerol ≫ anandamide [181]	1-arachidonoylglycerol > 2-arachidonoylglycerol > 1-oleoylglycerol > 2-oleoyl glycerol [375]
Selective inhibitors	orlistat (pIC_{50} 7.2) [40], RHC80267 (pIC_{50} 4.2) [255]	orlistat (pIC_{50} 7) [40], RHC80267	JJKK 048 (pIC_{50} 9.3) [1], KML29 (pIC_{50} 8.5) [77], JZL184 (pIC_{50} 8.1) [314]	WWL70 (pIC_{50} 7.2) [299], WWL123 (pIC_{50} 6.4) [21]
Comments	–	–	–	WWL70 has also been suggested to have activity at oxidative metabolic pathways independent of ABHD6 [513].

Comments on Endocannabinoid turnover: Many of the compounds described as inhibitors are irreversible and so potency estimates will vary with incubation time. FAAH2 is not found in rodents [563] and a few of the inhibitors described have been assessed at this enzyme activity. 2-arachidonoylglycerol has been reported to be hydrolysed by multiple enzyme activities from neural preparations, including *ABHD2* (P08910) [356], *ABHD12* (Q8N2K0) [44], neuropathy target esterase (*PNPLA6*, Q8IY17 [338]) and carboxylesterase 1 (*CES1*, P23141 [581]). *ABHD2* (P08910) has also been described as a triacylglycerol lipase and ester hydrolase [329], while *ABHD12* (Q8N2K0) is also able to hydrolyse lysophosphatidylserine [531]. *ABHD12* (Q8N2K0) has been described to be inhibited selectively by triterpenoids, such as betulinic acid [401].

Further reading on Endocannabinoid turnover

Blankman JL *et al.* (2013) Chemical probes of endocannabinoid metabolism. *Pharmacol. Rev.* **65**: 849-71 [PMID:23512546]

Janssen FJ *et al.* (2016) Inhibitors of diacylglycerol lipases in neurodegenerative and metabolic disorders. *Bioorg. Med. Chem. Lett.* **26**: 3831-7 [PMID:27394666]

Ueda N *et al.* (2013) Metabolism of endocannabinoids and related N-acylethanolamines: canonical and alternative pathways. *FEBS J.* **280**: 1874-94 [PMID:23425575]

Wellner N *et al.* (2013) N-acylation of phosphatidylethanolamine and its biological functions in mammals. *Biochim. Biophys. Acta* **1831**: 652-62 [PMID:23000428]

Eicosanoid turnover

Enzymes → Eicosanoid turnover

Overview: Eicosanoids are 20-carbon fatty acids, where the usual focus is the polyunsaturated analogue arachidonic acid and its metabolites. Arachidonic acid is thought primarily to derive from phospholipase A2 action on membrane phosphatidylcholine, and may be re-cycled to form phospholipid through conjugation with coenzyme A and subsequently glycerol derivatives. Oxidative metabolism of arachidonic acid is conducted through three major enzymatic routes: cyclooxygenases; lipoxygenases and cytochrome P450-like epoxygenases, particularly CYP2J2. Isoprostanes are structural analogues of the prostanoids (hence the nomenclature D-, E-, F-isoprostanes and isothromboxanes), which are produced in the presence of elevated free radicals in a non-enzymatic manner, leading to suggestions for their use as biomarkers of oxidative stress. Molecular targets for their action have yet to be defined.

Cyclooxygenase

Enzymes → Eicosanoid turnover → Cyclooxygenase

Overview: Prostaglandin (PG) G/H synthase, most commonly referred to as cyclooxygenase (COX, (5Z,8Z,11Z,14Z)-icosa-5,8,11,14-tetraenoate,hydrogen-donor : oxygen oxidoreductase) activity, catalyses the formation of PGG_2 from arachidonic acid. Hydroperoxidase activity inherent in the enzyme catalyses the formation of PGH_2 from PGG_2. COX-1 and -2 can be nonselectively inhibited by ibuprofen, ketoprofen, naproxen, indomethacin and paracetamol (acetaminophen). PGH_2 may then be metabolised to prostaglandins and thromboxanes by various prostaglandin synthases in an apparently tissue-dependent manner.

Nomenclature	COX-1	COX-2
HGNC, UniProt	*PTGS1*, P23219	*PTGS2*, P35354
EC number	1.14.99.1: Hydrogen donor + arachidonic acid + $2O_2$ = hydrogen acceptor + H_2O + PGH_2 arachidonic acid => PGG_2 => PGH_2 This enzyme is also associated with the following reaction:: docosahexaenoic acid => PGH_3	1.14.99.1: Hydrogen donor + arachidonic acid + $2O_2$ = hydrogen acceptor + H_2O + PGH_2 arachidonic acid => PGG_2 => PGH_2 This enzyme is also associated with the following reaction:: docosahexaenoic acid => PGH_3
Selective inhibitors	ketorolac (pIC_{50} 9.7) [557], FR122047 (pIC_{50} 7.5) [382]	celecoxib (pIC_{50} 8.7) [41], valdecoxib (pIC_{50} 8.3) [512], diclofenac (pIC_{50} 7.7) [45], rofecoxib (pIC_{50} 6.1–6.5) [557], lumiracoxib (pK_i 6.5) [46], meloxicam (pIC_{50} 6.3) [294], etoricoxib (pIC_{50} 6) [439]

Prostaglandin synthases

Enzymes → Eicosanoid turnover → Prostaglandin synthases

Overview: Subsequent to the formation of PGH_2, the cytochrome P450 activities thromboxane synthase (CYP5A1, *TBXAS1*, P24557 , EC 5.3.99.5) and prostacyclin synthase (CYP8A1, *PTGIS*, Q16647, EC 5.3.99.4) generate thromboxane A_2 and prostacyclin (PGI_2), respectively (see Cytochrome P450s). Additionally, multiple enzyme activities are able to generate prostaglandin E_2 (PGE_2), prostaglandin D_2 (PGD_2) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). PGD_2 can be metabolised to 9α,11β-prostacyclin $F_{2\alpha}$ through the multifunctional enzyme activity of AKR1C3. PGE_2 can be metabolised to 9α,11β-prostaglandin $F_{2\alpha}$ through the 9-ketoreductase activity of CBR1. Conversion of the 15-hydroxyecosanoids, including prostaglandins, lipoxins and leukotrienes to their keto derivatives by the NAD-dependent enzyme HPGD leads to a reduction in their biological activity.

Nomenclature	mPGES1	mPGES2	cPGES	L-PGDS
HGNC, UniProt	*PTGES*, O14684	*PTGES2*, Q9H7Z7	*PTGES3*, Q15185	*PTGDS*, P41222
EC number	5.3.99.3: PGH_2 = PGE_2	5.3.99.3: PGH_2 = PGE_2	5.3.99.3: PGH_2 = PGE_2	5.3.99.2: PGH_2 = PGD_2
Cofactors	glutathione	dihydrolipoic acid	–	–
Comments	–	–	Phosphorylated and activated by casein kinase 2 (CK2) [370]. Appears to regulate steroid hormone function by interaction with dimeric hsp90 [74, 253].	–

Nomenclature	H-PGDS	AKR1C3	CBR1	HPGD
HGNC, UniProt	*HPGDS*, O60760	*AKR1C3*, P42330	*CBR1*, P16152	*HPGD*, P15428
EC number	5.3.99.2: PGH_2 = PGD_2	1.3.1.20 1.1.1.188: PGD_2 + $NADP^+$ = $PGF_{2\alpha}$ + NADPH + H^+ 1.1.1.64 1.1.1.239 1.1.1.213	1.1.1.184 1.1.1.189: PGE_2 + $NADP^+$ = $PGF_{2\alpha}$ + NADPH + H^+ 1.1.1.197	1.1.1.141 15-hydroxyprostaglandins => 15-ketoprostaglandins LXA_4 => 15-keto-lipoxin A_4
Cofactors	–	$NADP^+$	$NADP^+$	–
Inhibitors	HQL-79 (pIC_{50} 5.3–5.5) [16]	tolfenamic acid (pK_i 8.1) [421] flufenamic acid, indomethacin, flavonoids [344, 484]	wedelolactone (pIC_{50} 5.4) [604]	
Comments	–	Also acts as a hydroxysteroid dehydrogenase activity.	–	–

Comments: YS121 has been reported to inhibit mPGES1 and 5-LOX with a pIC_{50} value of 5.5 [276].

Lipoxygenases

Enzymes → Eicosanoid turnover → Lipoxygenases

Overview: The lipoxygenases (LOXs) are a structurally related family of non-heme iron dioxygenases that function in the production, and in some cases metabolism, of fatty acid hydroperoxides. For arachidonic acid as substrate, these products are hydroperoxyeicosatetraenoic acids (HPETEs). In humans there are five lipoxygenases, the 5S-(arachidonate : oxygen 5-oxidoreductase), 12R-(arachidonate 12-lipoxygenase, 12R-type), 12S-(arachidonate : oxygen 12-oxidoreductase), and two distinct 15S-(arachidonate : oxygen 15-oxidoreductase) LOXs that oxygenate arachidonic acid in different positions along the carbon chain and form the corresponding 5S-, 12S-, 12R-, or 15S-hydroperoxides, respectively.

Nomenclature	5-LOX	12R-LOX	12S-LOX	15-LOX-1	15-LOX-2	E-LOX
HGNC, UniProt	*ALOX5*, P09917	*ALOX12B*, O75342	*ALOX12*, P18054	*ALOX15*, P16050	*ALOX15B*, O15296	*ALOXE3*, Q9BYJ1
EC number	1.13.11.34: arachidonic acid + O_2 = LTA_4 + H_2O	1.13.11.31 arachidonic acid + O_2 => 12R-HPETE	1.13.11.31 arachidonic acid + O_2 => 12S-HPETE	1.13.11.33: arachidonic acid + O_2 = 15S-HPETE linoleic acid + O_2 => 13S-HPODE	1.13.11.33: arachidonic acid + O_2 = 15S-HPETE	1.13.11.-

(continued)

Nomenclature	5-LOX	12R-LOX	12S-LOX	15-LOX-1	15-LOX-2	E-LOX
Endogenous substrates	arachidonic acid	–	–	–	–	12R-HPETE
Endogenous activators	5-LOX activating protein (*ALOX5AP*, P20292)	–	–	–	–	–
Endogenous inhibitors	Protein kinase A-mediated phosphorylation [324]	–	–	–	–	–
Selective inhibitors	CJ13610 (pIC_{50} 7.2) [144], PF-04191834 (pIC_{50} 6.6) [342], zileuton	–	–	compound 34 (pK_i >8) [425]	–	–
Comments	FLAP activity can be inhibited by MK-886 [124] and BAY-X1005 [210] leading to a selective inhibition of 5-LOX activity	–	–	–	–	E-LOX metabolises the product from the 12R-lipoxygenase (12R-HPETE) to a specific epoxyalcohol compound [592].

Comments: An 8-LOX (EC 1.13.11.40, arachidonate:oxygen 8-oxidoreductase) may be the mouse orthologue of 15-LOX-2 [167]. Some general LOX inhibitors are nordihydroguiaretic acid and esculetin. Zileuton and caffeic acid are used as 5-lipoxygenase inhibitors, while baicalein and CDC are 12-lipoxygenase inhibitors. The specificity of these inhibitors has not been rigorously assessed with all LOX forms: baicalein, along with other flavonoids, such as fisetin and luteolin, also inhibits 15-LOX-1 [450].

Leukotriene and lipoxin metabolism

Enzymes → Eicosanoid turnover → Leukotriene and lipoxin metabolism

Overview: Leukotriene A_4 (LTA_4), produced by 5-LOX activity, and lipoxins may be subject to further oxidative metabolism; ω-hydroxylation is mediated by CYP4F2 and CYP4F3, while β-oxidation in mitochondria and peroxisomes proceeds in a manner dependent on coenzyme A conjugation. Conjugation of LTA_4 at the 6 position with reduced glutathione to generate LTC_4 occurs under the influence of leukotriene C_4 synthase, with the subsequent formation of LTD_4 and LTE_4, all three of which are agonists at CysLT receptors. LTD_4 formation is catalysed by γ-glutamyltransferase, and subsequently dipeptidase 2 removes the terminal glycine from LTD_4 to generate LTE_4. Leukotriene A_4 hydrolase converts the 5,6-epoxide LTA_4 to the 5-hydroxylated LTB_4, an agonist for BLT receptors. LTA_4 is also acted upon by 12S-LOX to produce the trihydroxyeicosatetraenoic acids lipoxins LXA_4 and LXB_4. Treatment with a LTA_4 hydrolase inhibitor in a murine model of allergic airway inflammation increased LXA_4 levels, in addition to reducing LTB_4, in lung lavage fluid [429]. LTA_4 hydrolase is also involved in biosynthesis of resolvin Es. Aspirin has been reported to increase endogenous formation of 18S-hydroxyeicosapentaenoate (18S-HEPE) compared with 18R-HEPE, a resolvin precursor. Both enantiomers may be metabolised by human recombinant 5-LOX; recombinant LTA_4 hydrolase converted chiral 5S(6)-epoxide-containing intermediates to resolvin E1 and 18S-resolvin E1 [384].

Nomenclature	Leukotriene C4 synthase	γ-Glutamyltransferase	Dipeptidase 1	Dipeptidase 2
HGNC, UniProt	*LTC4S*, Q16873	*GGCT*, O75223	*DPEP1*, P16444	*DPEP2*, Q9H4A9
EC number	4.4.1.20: LTC_4 = glutathione + LTA_4	2.3.2.2: (5-L-glutamyl)-peptide + an amino acid = a peptide + a 5-L-glutamyl amino acid $LTC_4 + H_2O$ => LTD_4 + L-glutamate	3.4.13.19: $LTD_4 + H_2O = LTE_4$ + glycine	3.4.13.19: $LTD_4 + H_2O = LTE_4$ + glycine
Inhibitors	–	–	cilastatin (pK_i 6) [189]	–

Comments: LTA4H is a member of a family of arginyl aminopeptidases (ENSFM00250000001675), which also includes aminopeptidase B (*RNPEP*, 9H4A4) and aminopeptidase B-like 1 (*RNPEPL1*, Q9HAU8). Dipeptidase 1 and 2 are members of a family of membrane dipeptidases, which also includes (*DPEP3*, Q9H4B8) for which LTD_4 appears not to be a substrate.

Further reading on Eicosanoid turnover

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Grosser T *et al.* (2017) The Cardiovascular Pharmacology of Nonsteroidal Anti-Inflammatory Drugs. *Trends Pharmacol Sci* [PMID:28651847]

Horn T *et al.* (2015) Evolutionary aspects of lipoxygenases and genetic diversity of human leukotriene signaling. *Prog Lipid Res* **57**: 13-39 [PMID:25435097]

Joshi YB *et al.* (2015) The 12/15-lipoxygenase as an emerging therapeutic target for Alzheimer's disease. *Trends Pharmacol Sci* **36**: 181-6 [PMID:25708815]

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Patrignani P *et al.* (2015) Cyclooxygenase inhibitors: From pharmacology to clinical read-outs. *Biochim Biophys Acta* **1851**: 422-32 [PMID:25263946]

Radmark O *et al.* (2015) 5-Lipoxygenase, a key enzyme for leukotriene biosynthesis in health and disease. *Biochim Biophys Acta* **1851**: 331-9 [PMID:25152163]

Sasaki Y *et al.* (2017) Role of prostacyclin synthase in carcinogenesis. *Prostaglandins Other Lipid Mediat* [PMID:28506876]

Seo MJ *et al.* (2017) Prostaglandin synthases: Molecular characterization and involvement in prostaglandin biosynthesis. *Prog Lipid Res* **66**: 50-68 [PMID:28392405]

Vitale P *et al.* (2016) COX-1 Inhibitors: Beyond Structure Toward Therapy. *Med Res Rev* **36**: 641-71 [PMID:27111555]

GABA turnover

Enzymes → GABA turnover

Overview: The inhibitory neurotransmitter γ-aminobutyrate (GABA, 4-aminobutyrate) is generated in neurones by glutamic acid decarboxylase. GAD1 and GAD2 are differentially expressed during development, where GAD2 is thought to subserve a trophic role in early life and is distributed throughout the cytoplasm. GAD1 is expressed in later life and is more associated with nerve terminals [136] where GABA is principally accumulated in vesicles through the action of the vesicular inhibitory amino acid transporter SLC32A1. The role of γ-aminobutyraldehyde dehydrogenase (ALDH9A1) in neurotransmitter GABA synthesis is less clear. Following release from neurons, GABA may interact with either $GABA_A$ or $GABA_B$ receptors and may be accumulated in neurones and glia through the action of members of the SLC6 family of transporters. Successive metabolism through GABA transaminase and succinate semialdehyde dehydrogenase generates succinic acid, which may be further metabolized in the mitochondria in the tricarboxylic acid cycle.

Nomenclature	Glutamic acid decarboxylase 1	Glutamic acid decarboxylase 2
HGNC, UniProt	*GAD1*, Q99259	*GAD2*, Q05329
EC number	4.1.1.15: L-glutamic acid + H^+ -> GABA + CO_2	4.1.1.15: L-glutamic acid + H^+ -> GABA + CO_2
Common abreviation	GAD1	GAD2
Endogenous substrates	L-glutamic acid, L-aspartic acid	L-glutamic acid, L-aspartic acid
Products	GABA	GABA
Cofactors	pyridoxal phosphate	pyridoxal phosphate
Selective inhibitors	s-allylglycine	s-allylglycine
Comments	L-aspartic acid is a less rapidly metabolised substrate of mouse brain glutamic acid decarboxylase generating β-alanine [577]. Autoantibodies against GAD1 and GAD2 are elevated in type 1 diabetes mellitus and neurological disorders (see Further reading).	

Nomenclature	aldehyde dehydrogenase 9 family member A1	4-aminobutyrate aminotransferase	aldehyde dehydrogenase 5 family member A1
HGNC, UniProt	*ALDH9A1*, P49189	*ABAT*, P80404	*ALDH5A1*, P51649
EC number	1.2.1.19: 4-aminobutanal + NAD + H_2O = GABA + NADH + H^+ 1.2.1.47: 4-trimethylammoniobutanal + NAD + H_2O = 4-trimethylammoniobutanoate + NADPH + $2H^+$ 1.2.1.3: an aldehyde + H_2O + NAD = a carboxylate + $2H^+$ + NADH	2.6.1.19: GABA + α-ketoglutaric acid = L-glutamic acid + 4-oxobutanoate 2.6.1.22: (S)-3-amino-2-methylpropanoate + α-ketoglutaric acid = 2-methyl-3-oxopropanoate + L-glutamic acid	1.2.1.24: 4-oxobutanoate + NAD + H_2O = succinic acid + NADH + $2H^+$ 4-hydroxy-trans-2-nonenal + NAD + H_2O = 4-hydroxy-trans-2-nonenoate + NADH + $2H^+$
Common abreviation	–	GABA-T	SSADH
Cofactors	NAD	pyridoxal phosphate	NAD [469]
Inhibitors	–	vigabatrin (Irreversible inhibition) (pK_i 3.1) [306, 475]	4-acryloylphenol (pIC_{50} 6.5) [519]

Further reading on GABA turnover

Koenig MK *et al.* (2017) Phenotype of GABA-transaminase deficiency. *Neurology* **88**: 1919-1924 [PMID:28411234]

Lee H *et al.* (2015) Ornithine aminotransferase versus GABA aminotransferase: implications for the design of new anticancer drugs. *Med Res Rev* **35**: 286-305 [PMID:25145640]

McQuail JA *et al.* (2015) Molecular aspects of age-related cognitive decline: the role of GABA signaling. *Trends Mol Med* **21**: 450-60 [PMID:26070271]

Glycerophospholipid turnover

Enzymes → Glycerophospholipid turnover

Overview: Phospholipids are the basic barrier components of membranes in eukaryotic cells divided into glycerophospholipids (phosphatidic acid, phosphatidylethanolamine, phosphatidylcholine, phosphatidylserine, phosphatidylinositol and its phosphorylated derivatives) and sphingolipids (ceramide phosphorylcholine and ceramide phosphorylethanolamine).

Phosphoinositide-specific phospholipase C

Enzymes → Glycerophospholipid turnover → Phosphoinositide-specific phospholipase C

Overview: Phosphoinositide-specific phospholipase C (PLC, EC 3.1.4.11), catalyses the hydrolysis of PIP_2 to IP_3 and 1,2-diacylglycerol, each of which have major second messenger functions. Two domains, X and Y, essential for catalytic activity, are conserved in the different forms of PLC. Isoforms of PLC-β are activated primarily by G protein-coupled receptors through members of the $G_{q/11}$ family of G proteins. The receptor-mediated activation of PLC-γ involves their phosphorylation by receptor tyrosine kinases (RTK) in response to activation of a variety of growth factor receptors and immune system receptors. PLC-ϵ1 may represent a point of convergence of signalling via both G protein-coupled and catalytic receptors. Ca^{2+} ions are required for catalytic activity of PLC isoforms and have been suggested to be the major physiological form of regulation of PLC-δ activity. PLC has been suggested to be activated non-selectively by the small molecule *m*3M3FBS [23], although this mechanism of action has been questioned [284]. The aminosteroid U73122 has been described as an inhibitor of phosphoinositide-specific PLC [485], although its selectivity among the isoforms is untested and it has been reported to occupy the H1 histamine receptor [235].

Nomenclature	PLCβ1	PLCβ2	PLCβ3	PLCβ4	PLCγ1	PLCγ2
HGNC, UniProt	*PLCB1*, Q9NQ66	*PLCB2*, Q00722	*PLCB3*, Q01970	*PLCB4*, Q15147	*PLCG1*, P19174	*PLCG2*, P16885
Endogenous activators	Gαq, Gα11, Gβγ [220, 399, 487]	Gα16, Gβγ, Rac2 (*RAC2*, P15153) [65, 236, 237, 297, 399]	Gαq, Gβγ [71, 295, 399]	Gαq [196]	PIP_3 [22]	PIP_3, Rac1 (*RAC1*, P63000), Rac2 (*RAC2*, P15153), Rac3 (*RAC3*, P60763) [22, 411, 550]
Inhibitors	–	–	–	–	–	CCT129957 (pIC_{50} 5.5) [436]

Nomenclature	PLCδ1	PLCδ3	PLCδ4	PLCε1	PLCζ1	PLCη1	PLCη2
HGNC, UniProt	*PLCD1*, P51178	*PLCD3*, Q8N3E9	*PLCD4*, Q9BRC7	*PLCE1*, Q9P212	*PLCZ1*, Q86YW0	*PLCH1*, Q4KWH8	*PLCH2*, O75038
Endogenous activators	Transglutaminase II, p122-RhoGAP {Rat}, spermine, Gβγ [199, 226, 368, 399]	–	–	Ras, rho [490, 571]	–	–	Gβγ [600]
Endogenous inhibitors	Sphingomyelin [404]	–	–	–	–	–	–

Comments: A series of PLC-like proteins (*PLCL1*, Q15111; *PLCL2*, Q9UPR0 and *PLCH1*, Q4KWH8) form a family with PLCδ and PLCζ1 isoforms, but appear to lack catalytic activity. PLC-δ2 has been cloned from bovine sources [351].

Further reading on Phosphoinositide-specific phospholipase C

Cocco L *et al.* (2015) Phosphoinositide-specific phospholipase C in health and disease. *J Lipid Res* **56**: 1853-60 [PMID:25821234]

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Litosch I. (2015) Regulating G protein activity by lipase-independent functions of phospholipase C. *Life Sci* **137**: 116-24 [PMID:26239437]

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Swann K *et al.* (2016) The sperm phospholipase C-zeta and Ca2+ signalling at fertilization in mammals. *Biochem Soc Trans* **44**: 267-72 [PMID:26862214]

Phospholipase A_2

Enzymes → Glycerophospholipid turnover → Phospholipase A_2

Overview: Phospholipase A_2 (PLA_2, EC 3.1.1.4) cleaves the *sn*-2 fatty acid of phospholipids, primarily phosphatidylcholine, to generate lysophosphatidylcholine and arachidonic acid. Most commonly-used inhibitors (*e.g.* bromoenol lactone, arachidonyl trifluoromethyl ketone or methyl arachidonyl fluorophosphonate) are either non-selective within the family of phospholipase A_2 enzymes or have activity against other eicosanoid-metabolising enzymes.

Secreted or extracellular forms: $sPLA_2$-1B, $sPLA_2$-2A, $sPLA_2$-2D, $sPLA_2$-2E, $sPLA_2$-2F, $sPLA_2$-3, $sPLA_2$-10 and $sPLA_2$-12A

Cytosolic, calcium-dependent forms: $cPLA_2$-4A, $cPLA_2$-4B, $cPLA_2$-4C, $cPLA_2$-4D, $cPLA_2$-4E and $cPLA_2$-4F

Other forms: PLA_2-G5, $iPLA_2$-G6, PLA_2-G7 and PAFAH2 (platelet-activating factor acetylhydrolase 2)

Further reading on Phospholipase A2

Leslie CC. (2015) Cytosolic phospholipase A(2): physiological function and role in disease. *J Lipid Res* **56**: 1386-402 [PMID:25838312]

Ong WY *et al.* (2015) Synthetic and natural inhibitors of phospholipases A2: their importance for understanding and treatment of neurological disorders. *ACS Chem Neurosci* **6**: 814-31 [PMID:25891385]

Ramanadham S *et al.* (2015) Calcium-independent phospholipases A2 and their roles in biological processes and diseases. *J Lipid Res* **56**: 1643-68 [PMID:26023050]

Nomenclature	$sPLA_2$-1B	$sPLA_2$-2A	$sPLA_2$-2D	$sPLA_2$-2E	$sPLA_2$-2F	$sPLA_2$-3
HGNC, UniProt	*PLA2G1B*, P04054	*PLA2G2A*, P14555	*PLA2G2D*, Q9UNK4	*PLA2G2E*, Q9NZK7	*PLA2G2F*, Q9BZM2	*PLA2G3*, Q9NZ20

Nomenclature	cPLA$_2$-4A	cPLA$_2$-4B	cPLA$_2$-4C	cPLA$_2$-4D	cPLA$_2$-4E	cPLA$_2$-4F
HGNC, UniProt	*PLA2G4A*, P47712	*PLA2G4B*, P0C869	*PLA2G4C*, Q9UP65	*PLA2G4D*, Q86XP0	*PLA2G4E*, Q3MJ16	*PLA2G4F*, Q68DD2
EC number	3.1.1.4	3.1.1.4	3.1.1.4	3.1.1.4	3.1.1.4	3.1.1.4
Inhibitors	compound 57 (pIC$_{50}$ 8.4) [320]	–	–	–	–	–
Comments	cPLA$_2$-4A also expresses lysophospholipase (EC 3.1.1.5) activity [473].	–	–	–	–	–

Nomenclature	PLA$_2$-G5	iPLA$_2$-G6	PLA$_2$-G7	sPLA$_2$-10	sPLA$_2$-12A	platelet activating factor acetylhydrolase 2
HGNC, UniProt	*PLA2G5*, P39877	*PLA2G6*, O60733	*PLA2G7*, Q13093	*PLA2G10*, O15496	*PLA2G12A*, Q9BZM1	*PAFAH2*, Q99487
EC number	3.1.1.4	3.1.1.4	3.1.1.4	3.1.1.4	3.1.1.4	3.1.1.47
Inhibitors		–	darapladib (pIC$_{50}$ 10) [42]	–	–	–
Selective inhibitors			rilapladib (Competitive) (pIC$_{50}$ 9.6) [568]			

Comments: The sequence of PLA$_2$-2C suggests a lack of catalytic activity, while PLA$_2$-12B (GXIIB, GXIII sPLA$_2$-like) appears to be catalytically inactive [448]. A further fragment has been identified with sequence similarities to Group II PLA$_2$ members. Otoconin 90 (OC90) shows sequence homology to PLA$_2$-G10.

A binding protein for secretory phospholipase A$_2$ has been identified which shows modest selectivity for sPLA$_2$-1B over sPLA$_2$-2A, and also binds snake toxin phospholipase A$_2$ [13]. The binding protein appears to have clearance function for circulating secretory phospholipase A$_2$, as well as signalling functions, and is a candidate antigen for idiopathic membraneous nephropathy [29].

PLA$_2$-G7 and PAFAH2 also express platelet-activating factor acetylhydrolase activity (EC 3.1.1.47).

Phosphatidylcholine-specific phospholipase D

Enzymes → Glycerophospholipid turnover → Phosphatidylcholine-specific phospholipase D

Overview: Phosphatidylcholine-specific phospholipase D (PLD, EC 3.1.4.4) catalyses the formation of phosphatidic acid from phosphatidylcholine. In addition, the enzyme can make use of alcohols, such as butanol in a transphosphatidylation reaction [428].

Nomenclature	PLD1	PLD2
HGNC, UniProt	*PLD1*, Q13393	*PLD2*, O14939
EC number	3.1.4.4	3.1.4.4 A phosphatidylcholine + H_2O <=> choline + a phosphatidate
Endogenous activators	ADP-ribosylation factor 1 (*ARF1*, P84077), PIP_2, RhoA, PKC evoked phosphorylation, RalA [201, 323]	ADP-ribosylation factor 1 (*ARF1*, P84077), PIP_2 [316], oleic acid [454]
Endogenous inhibitors	Gβγ [418]	Gβγ [418]
Inhibitors	FIPI (pIC_{50} 8) [463]	FIPI (pIC_{50} 7.8) [484]
Selective inhibitors	compound 69 (pIC_{50} 7.3) [463]	VU0364739 (pIC_{50} 7.7) [293]

Comments: A lysophospholipase D activity (*ENPP2*, Q13822, also known as ectonucleotide pyrophosphatase/phosphodiesterase 2, phosphodiesterase I, nucleotide pyrophosphatase 2, autotaxin) has been described, which not only catalyses the production of lysophosphatidic acid (LPA) from lysophosphatidylcholine, but also cleaves ATP (see Goding *et al.*, 2003 [185]). Additionally, an N-acylethanolamine-specific phospholipase D (*NAPEPLD*, Q6IQ20) has been characterized, which appears to have a role in the generation of endocannabinoids/endovanilloids, including anandamide [388]. This enzyme activity appears to be enhanced by polyamines in the physiological range [311] and fails to transphosphatidylate with alcohols [408].
Three further, less well-characterised isoforms are PLD3 (*PLD3*, Q8IV08, other names Choline phosphatase 3, HindIII K4L homolog, Hu-K4), PLD4 (*PLD4*, Q96BZ4, other names Choline phosphatase 4, Phosphatidylcholine-hydrolyzing phospholipase, D4C14orf175 UNQ2488/PRO5775) and PLD5 (*PLD5*, Q8N7P1). PLD3 has been reported to be involved in myogenesis [391]. PLD4 is described not to have phospholipase D catalytic activity [588], but has been associated with inflammatory disorders [386, 507, 526]. Sequence analysis suggests that PLD5 is catalytically inactive.

Further reading on Phospholipase D

Brown HA *et al.* (2017) Targeting phospholipase D in cancer, infection and neurodegenerative disorders. *Nat Rev Drug Discov* **16**: 351-367 [PMID:28209987]
Frohman MA. (2015) The phospholipase D superfamily as therapeutic targets. *Trends Pharmacol Sci* **36**: 137-44 [PMID:25661257]
Nelson RK *et al.* (2015) Physiological and pathophysiological roles for phospholipase D. *J Lipid Res* **56**: 2229-37 [PMID:25926691]

Lipid phosphate phosphatases

Enzymes → Glycerophospholipid turnover → Lipid phosphate phosphatases

Overview: Lipid phosphate phosphatases, divided into phosphatidic acid phosphatases or lipins catalyse the dephosphorylation of phosphatidic acid (and other phosphorylated lipid derivatives) to generate inorganic phosphate and diacylglycerol. PTEN, a phosphatase and tensin homolog (BZS, MHAM, MMAC1, PTEN1, TEP1) is a phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase which acts as a tumour suppressor by reducing cellular levels of PI 3,4,5-P, thereby toning down activity of PDK1 and PKB. Loss-of-function mutations are frequently identified as somatic mutations in cancers.

Nomenclature	Lipin1	Lipin2	Lipin3	PPA2A	PPA2B	PPA3A	phosphatase and tensin homolog
HGNC, UniProt	*LPIN1*, Q14693	*LPIN2*, Q92539	*LPIN3*, Q9BQK8	*PLPP1*, O14494	*PLPP3*, O14495	*PLPP2*, O43688	*PTEN*, P60484
EC number	3.1.3.4	3.1.3.4	3.1.3.4	3.1.3.4	3.1.3.4	3.1.3.4	3.1.3.67 3.1.3.48 3.1.3.16
Substrates	–	phosphatidic acid	–	–	phosphatidic acid	–	phosphatidylinositol (3,4,5)-trisphosphate

Phosphatidylinositol kinases

Enzymes → Glycerophospholipid turnover → Phosphatidylinositol kinases

Overview:
Phosphatidylinositol may be phosphorylated at either 3- or 4-positions on the inositol ring by PI 3-kinases or PI 4-kinases, respectively.

Phosphatidylinositol 3-kinases

Phosphatidylinositol 3-kinases (PI3K, provisional nomenclature) catalyse the introduction of a phosphate into the 3-position of phosphatidylinositol (PI), phosphatidylinositol 4-phosphate (PIP) or phosphatidylinositol 4,5-bisphosphate (PIP_2). There is evidence that PI3K can also phosphorylate serine/threonine residues on proteins. In addition to the classes described below, further serine/threonine protein kinases, including ATM (Q13315) and mTOR (P42345), have been described to phosphorylate phosphatidylinositol and have been termed PI3K-related kinases. Structurally, PI3Ks have common motifs of at least one C2, calcium-binding domain and helical domains, alongside structurally-conserved catalytic domains. Wortmannin and LY 294002 are widely-used inhibitors of PI3K activities. Wortmannin is irreversible and shows modest selectivity between Class I and Class II PI3K, while LY294002 is reversible and selective for Class I compared to Class II PI3K.

Class I PI3Ks (EC 2.7.1.153) phosphorylate phosphatidylinositol 4,5-bisphosphate to generate phosphatidylinositol 3,4,5-trisphosphate and are heterodimeric, matching catalytic and regulatory subunits. Class IA PI3Ks include p110α, p110β and p110δ catalytic subunits, with predominantly p85 and p55 regulatory subunits. The single catalytic subunit that forms Class IB PI3K is p110γ. Class IA PI3Ks are more associated with receptor tyrosine kinase pathways, while the Class IB PI3K is linked more with GPCR signalling.

Class II PI3Ks (EC 2.7.1.154) phosphorylate phosphatidylinositol to generate phosphatidylinositol 3-phosphate (and possibly phosphatidylinositol 4-phosphate to generate phosphatidylinositol 3,4-bisphosphate). Three monomeric members exist, PI3K-C2α, β and β, and include Ras-binding, Phox homology and two C2domains.

The only **class III PI3K** isoform (EC 2.7.1.137) is a heterodimer formed of a catalytic subunit (VPS34) and regulatory subunit (VPS15).

Phosphatidylinositol 4-kinases

Phosphatidylinositol 4-kinases (EC 2.7.1.67) generate phosphatidylinositol 4-phosphate and may be divided into higher molecular weight type III and lower molecular weight type II forms.

1-phosphatidylinositol 4-kinase family

Enzymes → Kinases (EC 2.7.x.x) → Lipid modifying kinases → 1-phosphatidylinositol 4-kinase family

Nomenclature	phosphatidylinositol 4-kinase alpha	phosphatidylinositol 4-kinase beta
HGNC, UniProt	*PI4KA*, P42356	*PI4KB*, Q9UBF8
EC number	2.7.1.67	2.7.1.67
Common abreviation	PI4KIIIα/PIK4CA	PI4KIIIβ/PIK4CB
Endogenous activation	–	PKD-mediated phosphorylation [212]
Sub/family-selective inhibitors	wortmannin (pIC_{50} 6.7–6.8) [180, 352]	wortmannin (pIC_{50} 6.7–6.8) [180, 352]
Selective inhibitors	–	PIK-93 (pIC_{50} 7.7) [26, 271]

Phosphatidylinositol-4-phosphate 3-kinase family

Enzymes → Kinases (EC 2.7.x.x) → Lipid modifying kinases → Phosphatidylinositol-4-phosphate 3-kinase family

Nomenclature	phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 alpha	phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 beta	phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 gamma
HGNC, UniProt	*PIK3C2A*, O00443	*PIK3C2B*, O00750	*PIK3C2G*, O75747
EC number	2.7.1.154	2.7.1.154	2.7.1.154
Common abreviation	C2α/PIK3C2A	C2β/PIK3C2B	C2γ/PIK3C2G
Inhibitors	torin 2 (pIC_{50} 7.6) [312]	PI-103 (pIC_{50} 8) [213]	–

Enzymes → Glycerophospholipid turnover → Phosphatidylinositol phosphate kinases

Overview: PIP_2 is generated by phosphorylation of PI 4-phosphate or PI 5-phosphate by type I PI 4-phosphate 5-kinases or type II PI 5-phosphate 4-kinases.

Phosphatidylinositol 3-kinase family

Enzymes → Kinases (EC 2.7.x.x) → Lipid modifying kinases → Phosphatidylinositol 3-kinase family

Nomenclature	phosphatidylinositol 3-kinase catalytic subunit type 3
HGNC, UniProt	*PIK3C3*, Q8NEB9
EC number	2.7.1.137
Common abreviation	VPS34

Phosphatidylinositol-4,5-bisphosphate 3-kinase family

Enzymes → Kinases (EC 2.7.x.x) → Lipid modifying kinases → Phosphatidylinositol-4,5-bisphosphate 3-kinase family

Nomenclature	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta
HGNC, UniProt	*PIK3CA*, P42336	*PIK3CB*, P42338
EC number	2.7.1.153 2.7.11.1	2.7.1.153
Common abreviation	PI3Kα	PI3Kβ
Inhibitors	PIK-75 (pIC_{50} 9.5) [213], gedatolisib (pIC_{50} 9.4) [544], PF-04691502 (pK_i 9.2) [309], PI-103 (pIC_{50} 8.7) [435], BGT-226 (pIC_{50} 8.4) [337], KU-0060648 (pIC_{50} 8.4) [66], dactolisib (pIC_{50} 8.4) [332], apitolisib (pIC_{50} 8.3) [506]	KU-0060648 (pIC_{50} 9.3) [66], PI-103 (pIC_{50} 8.5) [435], AZD6482 (pIC_{50} 8) [380], ZSTK474 (pIC_{50} 7.4–7.8) [578, 583], apitolisib (pIC_{50} 7.6) [506], BGT-226 (pIC_{50} 7.2) [337]
Sub/family-selective inhibitors	pictilisib (pIC_{50} 8.5) [149]	pictilisib (pIC_{50} 7.5) [149]

Nomenclature	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta
HGNC, UniProt	*PIK3CG*, P48736	*PIK3CD*, O00329
EC number	2.7.1.153	2.7.1.153
Common abreviation	PI3Kγ	PI3Kδ
Inhibitors	dactolisib (pIC_{50} 8.3) [332], apitolisib (pIC_{50} 7.8) [506], PI-103 (pIC_{50} 7.8) [435], BGT-226 (pIC_{50} 7.4) [337], ZSTK474 (pIC_{50} 7.3–7.3) [578, 583], TG-100-115 (pIC_{50} 7.1) [394], alpelisib (pIC_{50} 6.6) [164], KU-0060648 (pIC_{50} 6.2) [66]	KU-0060648 (pIC_{50} >10) [66], idelalisib (*in vitro* activity against recombinant enzyme) (pIC_{50} 8.6) [290], PI-103 (pIC_{50} 8.5) [435], ZSTK474 (pIC_{50} 8.2–8.3) [578, 583], apitolisib (pIC_{50} 8.2) [506], dactolisib (pIC_{50} 8.1) [332], alpelisib (pIC_{50} 6.5) [164]
Sub/family-selective inhibitors	pictilisib (pIC_{50} 7.1) [149]	pictilisib (pIC_{50} 8.5) [149]
Selective inhibitors	CZC 24832 (pK_d 7.7) [32]	–

1-phosphatidylinositol-3-phosphate 5-kinase family

Enzymes → Kinases (EC 2.7.x.x) → Lipid modifying kinases → 1-phosphatidylinositol-3-phosphate 5-kinase family

Nomenclature	phosphoinositide kinase, FYVE-type zinc finger containing
HGNC, UniProt	*PIKFYVE*, Q9Y2I7
EC number	2.7.1.150: ATP + 1-phosphatidyl-1D-myo-inositol 3-phosphate = ADP + 1-phosphatidyl-1D-myo-inositol 3,5-bisphosphate

Type I PIP kinases (1-phosphatidylinositol-4-phosphate 5-kinase family)

Enzymes → Kinases (EC 2.7.x.x) → Lipid modifying kinases → Type I PIP kinases (1-phosphatidylinositol-4-phosphate 5-kinase family)

Overview: Type I PIP kinases are required for the production of the second messenger phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P2) by phosphorylating PtdIns(4)P [426]. This enzyme family is also known as type I PIP(5)Ks.

Nomenclature	phosphatidylinositol-4-phosphate 5-kinase type 1 alpha	phosphatidylinositol-4-phosphate 5-kinase type 1 gamma
HGNC, UniProt	*PIP5K1A*, Q99755	*PIP5K1C*, O60331
EC number	2.7.1.68	2.7.1.68
Common abreviation	PIP5K1A	PIP5K1C
Inhibitors	ISA-2011B [465]	–

Type II PIP kinases (1-phosphatidylinositol-5-phosphate 4-kinase family)

Enzymes → Kinases (EC 2.7.x.x) → Lipid modifying kinases → Type II PIP kinases (1-phosphatidylinositol-5-phosphate 4-kinase family)

Overview: Type II PIP kinases are essential for the production of the second messenger phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P2) by phosphorylating PtdIns(5)P [426]. This enzyme family is also known as type II PIP(5)Ks.

Nomenclature	phosphatidylinositol-5-phosphate 4-kinase type 2 alpha	phosphatidylinositol-5-phosphate 4-kinase type 2 beta	phosphatidylinositol-5-phosphate 4-kinase type 2 gamma
HGNC, UniProt	*PIP4K2A*, P48426	*PIP4K2B*, P78356	*PIP4K2C*, Q8TBX8
EC number	2.7.1.149 ATP + 1-phosphatidyl-1D-*myo*-inositol 5-phosphate <=> ADP + 1-phosphatidyl-1D-*myo*-inositol 4,5-bisphosphate	2.7.1.149	2.7.1.149
Common abreviation	PIP4K2A	PIP4K2B	PIP4K2C

Further reading on Phosphatidylinositol kinases

Bauer TM *et al.* (2015) Targeting PI3 kinase in cancer. *Pharmacol Ther* **146**: 53-60 [PMID:25240910]

Mayer IA *et al.* (2016) The PI3K/AKT Pathway as a Target for Cancer Treatment. *Annu Rev Med 67*: 11-28 [PMID:26473415]

Singh P *et al.* (2016) p110alpha and p110beta isoforms of PI3K signaling: are they two sides of the same coin? *FEBS Lett* **590**: 3071-82 [PMID:27552098]

Zhu J *et al.* (2015) Discovery of selective phosphatidylinositol 3-kinase inhibitors to treat hematological malignancies. *Drug Discov Today* **20**: 988-94 [PMID:25857437]

Further reading on Glycerophospholipid turnover

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Irvine RF. (2016) A short history of inositol lipids. *J Lipid Res* **57**: 1987-1994 [PMID:27623846]

Poli A *et al.* (2016) Nuclear Phosphatidylinositol Signaling: Focus on Phosphatidylinositol Phosphate Kinases and Phospholipases C. *J Cell Physiol* **231**: 1645-55 [PMID:26626942]

Haem oxygenase

Enzymes → Haem oxygenase

Overview: Haem oxygenase (heme,hydrogen-donor:oxygen oxidoreductase (α-methene-oxidizing, hydroxylating)), E.C. 1.14.99.3, converts heme into biliverdin and carbon monoxide, utilizing NADPH as cofactor.

Nomenclature	Haem oxygenase 1	Haem oxygenase 2
HGNC, UniProt	*HMOX1*, P09601	*HMOX2*, P30519
EC number	1.14.14.18 Protoheme + 3 [reduced NADPH-hemoprotein reductase] + 3 O(2) <=> biliverdin + Fe(2+) + CO + 3 [oxidized NADPH-hemoprotein reductase] + 3 H(2)O	1.14.14.18 Protoheme + 3 [reduced NADPH–hemoprotein reductase] + 3 O(2) <=> biliverdin + Fe(2+) + CO + 3 [oxidized NADPH–hemoprotein reductase] + 3 H(2)O
Common abreviation	HO1	HO2

Comments: The existence of a third non-catalytic version of haem oxygenase, HO3, has been proposed, although this has been suggested to be a pseudogene [215]. The chemical tin protoporphyrin IX acts as a haem oxygenase inhibitor in rat liver with an IC_{50} value of 11 nM [128].

Further reading on Haem oxygenase

Abraham NG *et al.* (2016) Translational Significance of Heme Oxygenase in Obesity and Metabolic Syndrome. *Trends Pharmacol Sci* **37**: 17-36 [PMID:26515032]

Naito Y *et al.* (2014) Heme oxygenase-1 and anti-inflammatory M2 macrophages. *Arch Biochem Biophys* **564**: 83-8 [PMID:25241054]

Otterbein LE *et al.* (2016) Heme Oxygenase-1 and Carbon Monoxide in the Heart: The Balancing Act Between Danger Signaling and Pro-Survival. *Circ Res* **118**: 1940-59 [PMID:27283533]

Poulos TL. (2014) Heme enzyme structure and function. *Chem. Rev.* **114**: 3919-62 [PMID:24400737]

Hydrogen sulphide synthesis

Enzymes → Hydrogen sulphide synthesis

Overview: Hydrogen sulfide is a gasotransmitter, with similarities to nitric oxide and carbon monoxide. Although the enzymes indicated below have multiple enzymatic activities, the focus here is the generation of hydrogen sulphide (H_2S) and the enzymatic characteristics are described accordingly. Cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE) are pyridoxal phosphate (PLP)-dependent enzymes. 3-mercaptopyruvate sulfurtransferase (3-MPST) functions to generate H_2S; only CAT is PLP-dependent, while 3-MPST is not. Thus, this third pathway is sometimes referred to as PLP-independent. CBS and CSE are predominantly cytosolic enzymes, while 3-MPST is found both in the cytosol and the mitochondria.

Nomenclature	Cystathionine β-synthase	Cystathionine γ-lyase	L-Cysteine:2-oxoglutarate aminotransferase	3-Mercaptopyruvate sulfurtransferase
HGNC, UniProt	*CBS*, P35520	*CTH*, P32929	*KYAT1*, Q16773	*MPST*, P25325
EC number	4.2.1.22	4.4.1.1	4.4.1.13	2.8.1.2
Common abreviation	CBS	CSE	CAT	MPST
Endogenous substrates	L-cysteine (K_m 6×10^{-3}M) [81], L-homocysteine	L-cysteine	L-cysteine	3-mercaptopyruvic acid (K_m 1.2×10^{-3}M) [369]
Products	cystathionine	NH_3, pyruvic acid	NH_3, pyruvic acid	pyruvic acid

(continued)

Nomenclature	Cystathionine β-synthase	Cystathionine γ-lyase	L-Cysteine:2-oxoglutarate aminotransferase	3-Mercaptopyruvate sulfurtransferase
Cofactors	pyridoxal phosphate	pyridoxal phosphate	pyridoxal phosphate	Zn^{2+}
Inhibitors	aminooxyacetic acid (pIC_{50} 5.1) [17]	aminoethoxyvinylglycine (pIC_{50} 6) [17], aminooxyacetic acid (pIC_{50} 6) [17], β-Cyano-L-alanine (pIC_{50} 5.8) [17], propargylglycine (pIC_{50} 4.4) [17]	–	–

Further reading on Hydrogen sulphide synthesis

Asimakopoulou A *et al.* (2013) Selectivity of commonly used pharmacological inhibitors for cystathionine á synthase (CBS) and cystathionine g lyase (CSE). *British Journal of Pharmacology* **169**: 922-932 [PM:23488457]

Kanagy NL *et al.* (2017) Vascular biology of hydrogen sulfide. *Am J Physiol Cell Physiol* **312**: C537-C549 [PMID:28148499]

Meng G *et al.* (2017) Protein S-sulfhydration by hydrogen sulfide in cardiovascular system. *Br J Pharmacol* [PMID:28148499]

Wallace JL *et al.* (2015) Hydrogen sulfide-based therapeutics: exploiting a unique but ubiquitous gasotransmitter. *Nat Rev Drug Discov* **14**: 329-45 [PMID:28148499]

Hydrolases

Enzymes → Hydrolases

Overview: Listed in this section are hydrolases not accumulated in other parts of the Concise Guide, such as monoacylglycerol lipase and acetylcholinesterase. Pancreatic lipase is the predominant mechanism of fat digestion in the alimentary system; its inhibition is associated with decreased fat absorption. CES1 is present at lower levels in the gut than CES2 (P23141), but predominates in the liver, where it is responsible for the hydrolysis of many aliphatic, aromatic and steroid esters. Hormone-sensitive lipase is also a relatively non-selective esterase associated with steroid ester hydrolysis and triglyceride metabolism, particularly in adipose tissue. Endothelial lipase is secreted from endothelial cells and regulates circulating cholesterol in high density lipoproteins.

Nomenclature	pancreatic lipase	lipase G, endothelial type	carboxylesterase 1	lipase E, hormone sensitive type
HGNC, UniProt	*PNLIP*, P16233	*LIPG*, Q9Y5X9	*CES1*, P23141	*LIPE*, Q05469
EC number	3.1.1.3	3.1.1.3	3.1.1.1	3.1.1.79
Common abreviation	PNLIP	LIPG	CES1	LIPE
Inhibitors	orlistat (pIC_{50} 8.9) [61]	–	–	–

Nomenclature	ectonucleoside triphosphate diphosphohydrolase 1	ectonucleoside triphosphate diphosphohydrolase 2
Systematic nomenclature	CD39	CD39L1
HGNC, UniProt	*ENTPD1*, P49961	*ENTPD2*, Q9Y5L3
EC number	3.6.1.5 Hydrolyzes NTPs to nucleotide monophosphates (NMPs): A nucleoside 5′-triphosphate + 2 H_2O <=> a nucleoside 5′-phosphate + 2 phosphate	3.6.1.- Hydrolyzes extracellular nucleotide 5′-triphosphates: NTP>NMP + 2 phosphate
Common abreviation	NTPDase-1	NTPDase-2
Selective inhibitors	–	PSB-6426 (pK_i 5.1) [53]
Comments	ENTPD1 sequentially converts extracellular purine nucleotides (ATP and ADP) to the monophosphate form. Adenosine is then generated by the action of Ecto-5′-Nucleotidase (CD73). ENTPD1 is the rate-limiting step. Extracellular ATP acts as a damage-associated molecular pattern (DAMP) that activates innate immune cells through adenosine-induced activation of P2X and P2Y purinogenic receptors.	–

Further reading on Hydrolases

Markey GM. (2011) Carboxylesterase 1 (Ces1): from monocyte marker to major player. *J. Clin. Pathol.* **64**: 107-9 [PMID:21177752]

Takenaka MC *et al.* (2016) Regulation of the T Cell Response by CD39. *Trends Immunol* **37**: 427-39 [PMID:27236363]

Inositol phosphate turnover

Enzymes → Inositol phosphate turnover

Overview: The sugar alcohol D-*myo*-inositol is a component of the phosphatidylinositol signalling cycle, where the principal second messenger is inositol 1,4,5-trisphosphate, IP_3, which acts at intracellular ligand-gated ion channels, IP_3 receptors to elevate intracellular calcium. IP_3 is recycled to inositol by phosphatases or phosphorylated to form other active inositol polyphosphates. Inositol produced from dephosphorylation of IP_3 is recycled into membrane phospholipid under the influence of phosphatidyinositol synthase activity (CDP-diacylglycerol-inositol 3-phosphatidyltransferase [EC 2.7.8.11]).

Inositol 1,4,5-trisphosphate 3-kinases

Enzymes → Inositol phosphate turnover → Inositol 1,4,5-trisphosphate 3-kinases

Overview: Inositol 1,4,5-trisphosphate 3-kinases (E.C. 2.7.1.127, ENSFM00250000001260) catalyse the generation of inositol 1,3,4,5-tetrakisphosphate (IP_4) from IP_3. IP_3 kinase activity is enhanced in the presence of calcium/calmodulin (*CALM1 CALM2 CALM3*, P62158) [98].

Information on members of this family may be found in the online database.

Inositol polyphosphate phosphatases

Enzymes → Inositol phosphate turnover → Inositol polyphosphate phosphatases

Overview: Members of this family exhibit phosphatase activity towards IP_3, as well as towards other inositol derivatives, including the phospholipids PIP_2 and PIP_3. With IP_3 as substrate, 1-phosphatase (EC 3.1.3.57) generates 4,5,-IP_2, 4-phosphatases (EC 3.1.3.66, ENSFM00250000001432) generate 1,5,-IP_2 and 5-phosphatases (E.C. 3.1.3.36 or 3.1.3.56) generate 1,4,-IP_2.

Information on members of this family may be found in the online database.

Comments: *In vitro* analysis suggested IP_3 and IP_4 were poor substrates for SKIP, synaptojanin 1 and synaptojanin 2, but suggested that PIP_2 and PIP_3 were more efficiently hydrolysed [458].

Inositol monophosphatase

Enzymes → Inositol phosphate turnover → Inositol monophosphatase

Overview: Inositol monophosphatase (E.C. 3.1.3.25, IMPase, *myo*-inositol-1(or 4)-phosphate phosphohydrolase) is a magnesium-dependent homodimer which hydrolyses *myo*-inositol monophosphate to generate *myo*-inositol and phosphate. Glycerol may be a physiological phosphate acceptor. Li^+ is a nonselective un-competitive inhibitor more potent at IMPase 1 (pK_i *ca.* 3.5, [347]; pIC_{50} 3.2, [385]) than IMPase 2 (pIC_{50} 1.8-2.1, [385]). IMPase activity may be inhibited competitively by L690330 (pK_i 5.5, [347]), although the enzyme selectivity is not yet established.

Nomenclature	IMPase 1	IMPase 2
HGNC, UniProt	*IMPA1*, P29218	*IMPA2*, O14732
EC number	3.1.3.25	3.1.3.25
Rank order of affinity	inositol 4-phosphate > inositol 3-phosphate > inositol 1-phosphate [347]	–
Inhibitors	Li^+ (pK_i 3.5) [347]	–

Comments: Polymorphisms in either of the genes encoding these enzymes have been linked with bipolar disorder [481, 482, 589]. Disruption of the gene encoding IMPase 1, but not IMPase 2, appears to mimic the effects of Li^+ in mice [104, 105].

Further reading on Inositol phosphate turnover

Irvine R. (2016) A tale of two inositol trisphosphates. *Biochem Soc Trans* **44**: 202-11 [PMID:26862207]

Livermore TM *et al.* (2016) Phosphate, inositol and polyphosphates. *Biochem Soc Trans* **44**: 253-9 [PMID:26862212]

Miyamoto A *et al.* (2017) Probes for manipulating and monitoring IP3. *Cell Calcium* **64**: 57-64 [PMID:27887748]

Windhorst S *et al.* (2017) Inositol-1,4,5-trisphosphate 3-kinase-A (ITPKA) is frequently over-expressed and functions as an oncogene in several tumor types. *Biochem Pharmacol* **137**: 1-9 [PMID:28377279]

Lanosterol biosynthesis pathway

Enzymes → Lanosterol biosynthesis pathway

Overview: Lanosterol is a precursor for cholesterol, which is synthesized primarily in the liver in a pathway often described as the mevalonate or HMG-CoA reductase pathway. The first two steps (formation of acetoacetyl CoA and the mitochondrial generation of (S)-3-hydroxy-3-methylglutaryl-CoA) are also associated with oxidation of fatty acids.

Nomenclature	acetyl-CoA acetyltransferase 1	acetyl-CoA acetyltransferase 2	hydroxymethylglutaryl-CoA synthase 1	hydroxymethylglutaryl-CoA synthase 2
HGNC, UniProt	*ACAT1*, P24752	*ACAT2*, Q9BWD1	*HMGCS1*, Q01581	*HMGCS2*, P54868
EC number	2.3.1.9: 2acetyl CoA = acetoacetyl CoA + coenzyme A	2.3.1.9: 2acetyl CoA = acetoacetyl CoA + coenzyme A	2.3.3.10: acetyl CoA + H_2O + acetoacetyl CoA -> (S)-3-hydroxy-3-methylglutaryl-CoA + coenzyme A	2.3.3.10: acetyl CoA + H_2O + acetoacetyl CoA -> (S)-3-hydroxy-3-methylglutaryl-CoA + coenzyme A
Comments	–	–	HMGCoA synthase is found in cytosolic (HMGCoA synthase 1) and mitochondrial (HMGCoA synthase 2) versions; the former associated with (R)-mevalonate synthesis and the latter with ketogenesis.	HMGCoA synthase is found in cytosolic (HMGCoA synthase 1) and mitochondrial (HMGCoA synthase 2) versions; the former associated with (R)-mevalonate synthesis and the latter with ketogenesis.

Nomenclature	hydroxymethylglutaryl-CoA reductase	mevalonate kinase	phosphomevalonate kinase	diphosphomevalonate decarboxylase
HGNC, UniProt	*HMGCR*, P04035	*MVK*, Q03426	*PMVK*, Q15126	*MVD*, P53602
EC number	1.1.1.34: (S)-3-hydroxy-3-methylglutaryl-CoA + NADPH -> (R)-mevalonate + coenzyme A + $NADP^+$ Reaction mechanism:: **First step:** (S)-3-hydroxy-3-methylglutaryl-CoA + NADPH -> mevaldyl-CoA + $NADP^+$ **Second step:** mevaldyl-CoA + H2O -> (R)-mevalonate + $NADP^+$	2.7.1.36: ATP + (R)-mevalonate -> ADP + (R)-5-phosphomevalonate	2.7.4.2: ATP + (R)-5-phosphomevalonate = ADP + (R)-5-diphosphomevalonate	4.1.1.33: ATP + (R)-5-diphosphomevalonate -> ADP + isopentenyl diphosphate + CO_2 + PO_3^{4-}
Inhibitors	lovastatin (Competitive) (pK_i 9.2) [10], rosuvastatin (Competitive) (pIC_{50} 8.3) [241], cerivastatin (Competitive) (pK_i 8.2) [67], atorvastatin (Competitive) (pIC_{50} 8.1) [241], cerivastatin (Competitive) (pIC_{50} 8) [528], simvastatin (Competitive) (pIC_{50} 8) [241], fluvastatin (Competitive) (pIC_{50} 7.6) [241]	–	–	–

(continued)

Nomenclature	hydroxymethylglutaryl-CoA reductase	mevalonate kinase	phosphomevalonate kinase	diphosphomevalonate decarboxylase
Comments	HMGCoA reductase is associated with intracellular membranes; enzymatic activity is inhibited by phosphorylation by AMP-activated kinase. The enzymatic reaction is a three-step reaction involving the intermediate generation of mevaldehyde-CoA and mevaldehyde.	Mevalonate kinase activity is regulated by the downstream products farnesyl diphosphate and geranyl diphosphate as an example of feedback inhibition.	–	–

Nomenclature	isopentenyl-diphosphate Δ-isomerase 1	isopentenyl-diphosphate Δ-isomerase 2	geranylgeranyl diphosphate synthase
HGNC, UniProt	*IDI1*, Q13907	*IDI2*, Q9BXS1	*GGPS1*, O95749
EC number	5.3.3.2: isopentenyl diphosphate = dimethylallyl diphosphate	5.3.3.2: isopentenyl diphosphate = dimethylallyl diphosphate	2.5.1.29: trans,trans-farnesyl diphosphate + isopentenyl diphosphate -> geranylgeranyl diphosphate + diphosphate 2.5.1.10: geranyl diphosphate + isopentenyl diphosphate -> trans,trans-farnesyl diphosphate + diphosphate 2.5.1.1: dimethylallyl diphosphate + isopentenyl diphosphate = geranyl diphosphate + diphosphate

Nomenclature	farnesyl diphosphate synthase	squalene synthase	squalene monooxygenase	lanosterol synthase
HGNC, UniProt	*FDPS*, P14324	*FDFT1*, P37268	*SQLE*, Q14534	*LSS*, P48449
EC number	2.5.1.10: geranyl diphosphate + isopentenyl diphosphate -> trans,trans-farnesyl diphosphate + diphosphate 2.5.1.1: dimethylallyl diphosphate + isopentenyl diphosphate = geranyl diphosphate + diphosphate	2.5.1.21: 2trans,trans-farnesyl diphosphate -> presqualene diphosphate + diphosphate presqualene diphosphate + NAD(P)H + H^+ -> squalene + diphosphate + $NAD(P)^+$	1.14.13.132: H^+ + NADPH + O_2 + squalene = H_2O + $NADP^+$ + (*S*)-2,3-epoxysqualene	5.4.99.7: (*S*)-2,3-epoxysqualene = lanosterol
Cofactors	–	NADPH	–	–
Inhibitors	risedronate (pIC_{50} 8.4) [33], zoledronic acid (pK_i 7.1) [129], alendronate (pIC_{50} 6.3) [33]	zaragozic acid A (pK_i 10.1) [34] – Rat, zaragozic acid A (pIC_{50} 9.2) [530]		–
Selective inhibitors	ibandronic acid (pK_i 6.7) [129], pamidronic acid (pIC_{50} 6.7) [129]	–	–	–

Further reading on Lanosterol biosynthesis pathway

Moutinho M *et al.* (2017) The mevalonate pathway in neurons: It's not just about cholesterol. *Exp Cell Res* [PMID:28232115]
Mullen PJ *et al.* (2016) The interplay between cell signalling and the mevalonate pathway in cancer. *Nat Rev Cancer* **16**: 718-731 [PMID:27562463]
Ness GC. (2015) Physiological feedback regulation of cholesterol biosynthesis: Role of translational control of hepatic HMG-CoA reductase and possible involvement of oxylanosterols. *Biochim Biophys Acta* **1851**: 667-73 [PMID:25701719]
Porter TD. (2015) Electron Transfer Pathways in Cholesterol Synthesis. *Lipids* **50**: 927-36 [PMID:26344922]
Samaras K *et al.* (2016) Does statin use cause memory decline in the elderly? *Trends Cardiovasc Med* **26**: 550-65 [PMID:27177529]

Nucleoside synthesis and metabolism

Enzymes → Nucleoside synthesis and metabolism

Overview: The *de novo* synthesis and salvage of nucleosides have been targetted for therapeutic advantage in the treatment of particular cancers and gout. Dihydrofolate reductase produces tetrahydrofolate, a cofactor required for synthesis of purines, pyrimidines and amino acids. GART allows formylation of phosphoribosylglycinamide, an early step in purine biosynthesis. Dihydroorotate dehydrogenase produces orotate, a key intermediate in pyrimidine synthesis. IMP dehydrogenase generates xanthosine monophosphate, an intermediate in GTP synthesis.

Nomenclature	dihydrofolate reductase	dihydroorotate dehydrogenase (quinone)	inosine monophosphate dehydrogenase 1	inosine monophosphate dehydrogenase 2	xanthine dehydrogenase
HGNC, UniProt	*DHFR*, P00374	*DHODH*, Q02127	*IMPDH1*, P20839	*IMPDH2*, P12268	*XDH*, P47989
EC number	1.5.1.3	1.3.5.2	1.1.1.205	1.1.1.205	1.17.1.4
Inhibitors	pemetrexed (pK_i 8.1) [171, 474], pralatrexate (pK_i 7.3) [244]	teriflunomide (pK_i 7.5) [214], leflunomide (pK_i 4.9) [397]	mycophenolic acid (pIC_{50} 7.7) [376], ribavirin (pIC_{50} 5.6–6) [572], thioguanine [132, 546]	mycophenolic acid (pIC_{50} 7.7) [376], ribavirin (pIC_{50} 5.6–6) [572], thioguanine [132, 546]	febuxostat (pK_i 9.9) [387] – Bovine, allopurinol (pK_i 5.2) [36]
Selective inhibitors	methotrexate (pK_i 8.9) [446]	–	–	–	–

Nomenclature	ribonucleotide reductase catalytic subunit M1	ribonucleotide reductase regulatory subunit M2	ribonucleotide reductase regulatory TP53 inducible subunit M2B	thymidylate synthetase	phosphoribosylglycinamide formyltransferase, phosphoribosylglycinamide synthetase, phosphoribosylaminoimidazole synthetase	purine nucleoside phosphorylase
HGNC, UniProt	*RRM1*, P23921	*RRM2*, P31350	*RRM2B*, Q7LG56	*TYMS*, P04818	*GART*, P22102	*PNP*, P00491
EC number	1.17.14.1	1.17.4.1	1.17.1.4	2.1.1.45	2.1.2.2 6.3.3.1 6.3.4.13	–
Common abreviation	–	–	–	–	GART	–
Inhibitors	clofarabine (pIC_{50} 8.3) [400], fludarabine (pIC_{50} 6) [534], hydroxyurea (pIC_{50} 3.8) [471], gemcitabine [219]		–	pemetrexed (pK_i 7) [474], capecitabine [69, 398]	pemetrexed (pK_i 5) [474] – Mouse	–
Selective inhibitors	–	–	–	raltitrexed (pIC_{50} 6.5) [172]	–	–

Comments: Thymidylate synthetase allows the interconversion of dUMP and dTMP, thereby acting as a crucial step in DNA synthesis. Purine nucleoside phosphorylase allows separation of a nucleoside into the nucleobase and ribose phosphate for nucleotide salvage. Xanthine dehydrogenase generates urate in the purine degradation pathway. Post-translational modifications of xanthine dehydrogenase convert the enzymatic reaction to a xanthine oxidase, allowing the interconversion of hypoxanthine and xanthine, with the production (or consumption) of reactive oxygen species. Ribonucleotide reductases allow the production of deoxyribonucleotides from ribonucleotides.

Further reading on Nucleoside synthesis and metabolism

Day RO *et al.* (2016) Xanthine oxidoreductase and its inhibitors: relevance for gout. *Clin Sci (Lond)* **130**: 2167-2180 [PMID:27798228]

Okafor ON *et al.* (2017) Allopurinol as a therapeutic option in cardiovascular disease. *Pharmacol Ther* **172**: 139-150 [PMID:27916655]

Sramek M *et al.* (2017) Much more than you expected: The non-DHFR-mediated effects of methotrexate. *Biochim Biophys Acta* **1861**: 499-503 [PMID:27993660]

Sphingosine 1-phosphate turnover

Enzymes → Sphingosine 1-phosphate turnover

Overview: S1P (sphingosine 1-phosphate) is a pro-survival signal, in contrast to ceramide. It is formed by the sphingosine kinase-catalysed phosphorylation of sphingosine. S1P can be released from cells to act as an agonist at a family of five G protein-coupled receptors ($S1P_{1-5}$) but also has intracellular targets. S1P can be dephosphorylated back to sphingosine or hydrolysed to form hexadecanal and phosphoethanolamine. Sphingosine choline phosphotransferase (EC 2.7.8.10) generates sphingosylphosphocholine from sphingosine and CDP-choline. Sphingosine β-galactosyltransferase (EC 2.4.1.23) generates psychosine from sphingosine in the presence of UDP-α-D-galactose. The molecular identities of these enzymes have not been confirmed.

Sphingosine kinase

Enzymes → Sphingosine 1-phosphate turnover → Sphingosine kinase

Nomenclature	sphingosine kinase 1	sphingosine kinase 2
HGNC, UniProt	*SPHK1*, Q9NYA1	*SPHK2*, Q9NRA0
EC number	2.7.1.91: sphingosine + ATP = sphingosine 1-phosphate + ADP ATP + sphinganine = sphinganine 1-phosphate + ADP	2.7.1.91: sphingosine + ATP = sphingosine 1-phosphate + ADP ATP + sphinganine = sphinganine 1-phosphate + ADP
Common abreviation	SPHK1	SPHK2
Cofactors	Mg^{2+} [469]	Mg^{2+}
Sub/family-selective inhibitors	SKI-II (pIC_{50} 6.3) [156]	–
Selective inhibitors	PF-543 (pIC8.7) [556],	ABC294640 (pK_i 5) [157], ROMe (pIC_{50} 4.6) [304]

Further reading on Sphingosine kinases

Adams DR *et al.* (2016) Sphingosine Kinases: Emerging Structure-Function Insights. *Trends Biochem Sci* **41**: 395-409 [PMID:27021309]
Marfe G *et al.* (2015) Sphingosine kinases signalling in carcinogenesis. *Mini Rev Med Chem* **15**: 300-14 [PMID:25723458]
Pyne NJ *et al.* (2017) Sphingosine Kinase 2 in Autoimmune/Inflammatory Disease and the Development of Sphingosine Kinase 2 Inhibitors. *Trends Pharmacol Sci* **38**: 581-591 [PMID:28606480]
Pyne S *et al.* (2016) Sphingosine 1-phosphate and sphingosine kinases in health and disease: Recent advances. *Prog Lipid Res* **62**: 93-106 [PMID:26970273]
Santos WL *et al.* (2015) Drugging sphingosine kinases. *ACS Chem Biol* **10**: 225-33 [PMID:25384187]

Sphingosine 1-phosphate phosphatase

Enzymes → Sphingosine 1-phosphate turnover → Sphingosine 1-phosphate phosphatase

Nomenclature	sphingosine-1-phosphate phosphatase 1	sphingosine-1-phosphate phosphatase 2
HGNC, UniProt	*SGPP1*, Q9BX95	*SGPP2*, Q8IWX5
EC number	3.1.3.-: sphingosine 1-phosphate -> sphingosine + inorganic phosphate	3.1.3.-: sphingosine 1-phosphate -> sphingosine + inorganic phosphate
Common abreviation	SGPP1	SGPP2
Comments	Depletion of S1P phosphohydrolase-1 (SPP1), which degrades intracellular S1P, induces the unfolded protein response and endoplasmic reticulum stress-induced autophagy [231].	–

Sphingosine 1-phosphate lyase

Enzymes → Sphingosine 1-phosphate turnover → Sphingosine 1-phosphate lyase

Nomenclature	sphingosine-1-phosphate lyase 1
HGNC, UniProt	*SGPL1*, O95470
EC number	4.1.2.27: sphingosine 1-phosphate -> phosphoethanolamine + hexadecanal
Cofactors	pyridoxal phosphate
Inhibitors	compound 31 (pIC_{50} 6.7) [564]
Comments	THI (2-Acetyl-5-tetrahydroxybutyl imidazole) inhibits the enzyme activity in intact cell preparations [462].

Further reading on Sphingosine 1-phosphate lyase

Ebenezer DL *et al.* (2016) Targeting sphingosine-1-phosphate signaling in lung diseases. *Pharmacol Ther* **168**: 143-157 [PMID:27621206]

Sanllehi P *et al.* (2016) Inhibitors of sphingosine-1-phosphate metabolism (sphingosine kinases and sphingosine-1-phosphate lyase). *Chem Phys Lipids* **197**: 69-81 [PMID:26200919]

Thyroid hormone turnover

Enzymes → Thyroid hormone turnover

Overview:
The thyroid hormones triiodothyronine and thyroxine, usually abbreviated as triiodothyronine and T_4, respectively, are synthesized in the thyroid gland by sequential metabolism of tyrosine residues in the glycosylated homodimeric protein thyroglobulin (*TG*, P01266) under the influence of the haem-containing protein iodide peroxidase. Iodide peroxidase/TPO is a haem-containing enzyme, from the same structural family as eosinophil peroxidase (*EPX*, P11678), lactoperoxidase (LPO, P22079) and myeloperoxidase (MPO, P05164). Circulating thyroid hormone is bound to thyroxine-binding globulin (SERPINA7, P05543).

Nomenclature	thyroid peroxidase
HGNC, UniProt	*TPO*, P07202
EC number	1.11.1.8: [Thyroglobulin]-L-tyrosine + H_2O_2 + H^+ + I^- -> [Thyroglobulin]-3,5,3′-triiodo-L-thyronine + [thyroglobulin]-aminoacrylate + H_2O
Common abreviation	TPO
Cofactors	Ca^{2+}
Inhibitors	methimazole [373], propylthiouracil [373]
Comments	Carbimazole is a pro-drug for methimazole

Tissue deiodinases
These are 1 TM selenoproteins that remove an iodine from T_4 (3,3′,5,5′-tetraiodothyronine) to generate triiodothyronine (3,3′,5-triiodothyronine, a more potent agonist at thyroid hormone receptors) or rT_3 (rT3, 3,3′,5′-triiodothyronine, a relatively inactive analogue). DIO1 is also able to deiodinate RT3 to form 3,3′-diidothyronine (T_2). Iodotyrosine deiodinase is a 1TM homodimeric enzyme.

Nomenclature	iodothyronine deiodinase 1	iodothyronine deiodinase 2	iodothyronine deiodinase 3	iodotyrosine deiodinase
HGNC, UniProt	*DIO1*, P49895	*DIO2*, Q92813	*DIO3*, P55073	*IYD*, Q6PHW0
EC number	1.97.1.10: T_4 -> triiodothyronine rT_3 -> T_2	1.97.1.10: T_4 -> triiodothyronine rT_3 -> T_2	1.97.1.11: T_4 -> triiodothyronine rT_3 -> T_2	1.22.1.1: 3-iodotyrosine -> L-tyrosine + I^- 3,5-diiodo-L-tyrosine -> 3-iodotyrosine + I^-
Common abreviation	DIO1	DIO2	DIO3	IYD
Cofactors	–	–	–	flavin adenine dinucleotide, NADPH

Further reading on Thyroid hormone turnover

Darras VM *et al.* (2015) Intracellular thyroid hormone metabolism as a local regulator of nuclear thyroid hormone receptor-mediated impact on vertebrate development. *Biochim. Biophys. Acta* **1849**: 130-41 [PMID:24844179]
Gereben B *et al.* (2015) Scope and limitations of iodothyronine deiodinases in hypothyroidism. *Nat Rev Endocrinol* **11**: 642-52 [PMID:26416219]
Mondal S *et al.* (2017) Novel thyroid hormone analogues, enzyme inhibitors and mimetics, and their action. *Mol Cell Endocrinol* [PMID:28408161]
Schweizer U *et al.* (2015) New insights into the structure and mechanism of iodothyronine deiodinases. *J Mol Endocrinol* **55**: R37-52 [PMID:26390881]
van der Spek AH *et al.* (2017) Thyroid hormone metabolism in innate immune cells. *J Endocrinol* **232**: R67-R81 [PMID:27852725]

1.14.11.29 2-oxoglutarate oxygenases

Enzymes → 1.14.11.29 2-oxoglutarate oxygenases

Overview: Hypoxia inducible factor (HIF) is a transcriptional complex that is involved in oxygen homeostasis [466]. At normal oxygen levels, the alpha subunit of HIF (HIF-1α) is targeted for degradation by prolyl hydroxylation by the prolyl hydrolxyases PHD proteins 1-3 (HIF-PHs) whch are 2-oxoglutarate oxygenases responsible for the post-translational modification of a specific proline in each of the oxygen-dependent degradation domains of HIF-1α. Hydroxylated HIFs are then targeted for proteasomal degradation *via* the von Hippel-Lindau ubiquitination complex [245]. Under hypoxic conditions, the hydroxylation reaction is blunted which results in decreased HIF degradation. The surviving HIFs are then available to translocate to the nucleus where they heterodimerize with HIF-1β, effecting increased expression of hypoxia-inducible genes.

HIF-PH enzymes are being investigated as pharmacological targets as their inhibition mimics the hypoxic state and switches on transcription of genes associated with processes such as erythropoiesis and vasculogenesis [151]. Small molecule HIF-PH inhibitors are in clinical trial as novel therapies for the amelioration of anemia associated with chronic kidney disease [50].

Nomenclature	egl-9 family hypoxia inducible factor 2	egl-9 family hypoxia inducible factor 1	egl-9 family hypoxia inducible factor 3
HGNC, UniProt	*EGLN2*, Q96KS0	*EGLN1*, Q9GZT9	*EGLN3*, Q9H6Z9
EC number	–	1.14.11.29	1.14.11.29
Common abreviation	PHD1	PHD2	PHD3
Inhibitors		IOX2 (pIC_{50} 7.7) [91]	

Further reading on 2-oxoglutarate oxygenases

Ivan M *et al.* (2017) The EGLN-HIF O2-Sensing System: Multiple Inputs and Feedbacks. *Mol Cell* **66**: 772-779 [PMID:28622522]
Markolovic S *et al.* (2015) Protein Hydroxylation Catalyzed by 2-Oxoglutarate-dependent Oxygenases. *J Biol Chem* **290**: 20712-22 [PMID:26152730]
Salminen A *et al.* (2015) 2-Oxoglutarate-dependent dioxygenases are sensors of energy metabolism, oxygen availability, and iron homeostasis: potential role in the regulation of aging process. *Cell Mol Life Sci* **72**: 3897-914 [PMID:26118662]
Wu Y *et al.* (2017) Application of in-vitro screening methods on hypoxia inducible factor prolyl hydroxylase inhibitors. *Bioorg Med Chem* **25**: 3891-3899 [PMID:28625716]
Zurlo G *et al.* (2016) New Insights into Protein Hydroxylation and Its Important Role in Human Diseases. *Biochim Biophys Acta* **1866**: 208-220 [PMID:27663420]

1.14.13.9 kynurenine 3-monooxygenase

Enzymes → 1.14.13.9 kynurenine 3-monooxygenase

Nomenclature	Kynurenine 3-monooxygenase
HGNC, UniProt	*KMO*, O15229
EC number	1.14.13.9 L-kynurenine + NADPH + O_2 <=> 3-hydroxy-L-kynurenine + NADP(+) + H_2O
Comments	Kynurenine 3-monooxygenase participates in metabolism of the essential amino acid tryptophan.

Further reading on Kynurenine 3-monooxygenases

Dounay AB *et al.* (2015) Challenges and Opportunities in the Discovery of New Therapeutics Targeting the Kynurenine Pathway. *J Med Chem* **58**: 8762-82 [PMID:26207924]
Erhardt S *et al.* (2017) The kynurenine pathway in schizophrenia and bipolar disorder. *Neuropharmacology* **112**: 297-306 [PMID:27245499]
Fujigaki H *et al.* (2017) L-Tryptophan-kynurenine pathway enzymes are therapeutic target for neuropsychiatric diseases: Focus on cell type differences. *Neuropharmacology* **112**: 264-274 [PMID:26767951]
Smith JR *et al.* (2016) Kynurenine-3-monooxygenase: a review of structure, mechanism, and inhibitors. *Drug Discov Today* **21**: 315-24 [PMID:26589832]
Song P *et al.* (2017) Abnormal kynurenine pathway of tryptophan catabolism in cardiovascular diseases. *Cell Mol Life Sci* **74**: 2899-2916 [PMID:28314892]

2.4.2.30 poly(ADP-ribose)polymerases

Enzymes → 2.4.2.30 poly(ADP-ribose)polymerases

Overview: The Poly ADP-ribose polymerase family is a series of enzymes, where the best characterised members are nuclear proteins which are thought to function by binding to single strand breaks in DNA, allowing the recruitment of repair enzymes by the synthesis of NAD-derived ADP-ribose polymers, which are subsequently degraded by a glycohydrolase (*PARG*, Q86W56).

Nomenclature	poly(ADP-ribose) polymerase 1	poly(ADP-ribose) polymerase 2	poly (ADP-ribose) polymerase 3
HGNC, UniProt	*PARP1*, P09874	*PARP2*, Q9UGN5	*PARP3*, Q9Y6F1
EC number	2.4.2.30	2.4.2.30	–
Common abreviation	PARP1	PARP2	PARP3
Selective inhibitors	AG14361 (pK_i 8.2) [483]	–	–

Further reading on Poly(ADP-ribose)polymerases

Bai P. (2015) Biology of Poly(ADP-Ribose) Polymerases: The Factotums of Cell Maintenance. *Mol Cell* **58**: 947-58 [PMID:26091343]

Bai P *et al*. (2015) Poly(ADP-ribose) polymerases as modulators of mitochondrial activity. *Trends Endocrinol Metab* **26**: 75-83 [PMID:25497347]

Bock FJ *et al*. (2016) New directions in poly(ADP-ribose) polymerase biology. *FEBS J* **283**: 4017-4031 [PMID:27087568]

Bock FJ *et al*. (2015) RNA Regulation by Poly(ADP-Ribose) Polymerases. *Mol Cell* **58**: 959-69 [PMID:26091344]

Ryu KW *et al*. (2015) New facets in the regulation of gene expression by ADP-ribosylation and poly(ADP-ribose) polymerases. *Chem Rev* **115**: 2453-81 [PMID:25575290]

2.5.1.58 Protein farnesyltransferase

Enzymes → 2.5.1.58 Protein farnesyltransferase

Overview: Farnesyltransferase is a member of the prenyltransferases family which also includes geranylgeranyltransferase types I (EC 2.5.1.59) and II (EC 2.5.1.60) [72]. Protein farnesyltransferase catalyses the post-translational formation of a thioether linkage between the C-1 of an isoprenyl group and a cysteine residue fourth from the C-terminus of a protein (*ie* to the CaaX motif, where 'a' is an aliphatic amino acid and 'X' is usually serine, methionine, alanine or glutamine; leucine for EC 2.5.1.59) [165]. Farnesyltransferase is a dimer, composed of an alpha and beta subunit and requires Mg^{2+} and Zn^{2+} ions as co-factors. The active site is located between the subunits. Prenylation creates a hydrophobic domain on protein tails which acts as a membrane anchor.

Substrates of the prenyltransferases include Ras, Rho, Rab, other Ras-related small GTP-binding proteins, G-protein γ-subunits, nuclear lamins, centromeric proteins and many proteins involved in visual signal transduction.

In relation to the causative association between oncogenic Ras proteins and cancer, farnesyltransferase has become an important mechanistic drug discovery target.

Information on members of this family may be found in the online database.

Further reading on Protein farnesyltransferase

Gao S *et al.* (2016) The Role of Geranylgeranyltransferase I-Mediated Protein Prenylation in the Brain. *Mol Neurobiol* **53**: 6925-6937 [PMID:26666664]
Shen M *et al.* (2015) Farnesyltransferase and geranylgeranyltransferase I: structures, mechanism, inhibitors and molecular modeling. *Drug Discov Today* **20**: 267-76 https://www.ncbi.nlm.nih.gov/pubmed/25450772[PMID:25450772]
Shen Y *et al.* (2015) The Recent Development of Farnesyltransferase Inhibitors as Anticancer and Antimalarial Agents. *Mini Rev Med Chem 15*: 837-57 [PMID:25963569]
Wang M *et al.* (2016) Protein prenylation: unique fats make their mark on biology. *Nat Rev Mol Cell Biol* **17**: 110-22 [PMID:26790532]

3.5.1.- Histone deacetylases (HDACs)

Enzymes → 3.5.1.- Histone deacetylases (HDACs)

Overview: Histone deacetylases act as erasers of epigenetic acetylation marks on lysine residues in histones. Removal of the acetyl groups facilitates tighter packing of chromatin (heterochromatin formation) leading to transcriptional repression.
The histone deacetylase family has been classified in to five subfamilies based on phylogenetic comparison with yeast homologues:
Class I contains HDACs 1, 2, 3 and 8
Class IIa contains HDACs 4, 5, 7 and 9
Class IIb contains HDACs 6 and 10
Class III contains the sirtuins (SIRT1-7)
Class IV contains only HDAC11.
Classes I, II and IV use Zn^+ as a co-factor, whereas catalysis by Class III enzymes requires NAD^+ as a co-factor, and members of this subfamily have ADP-ribosylase activity in addition to protein deacetylase function [456].
HDACs have more general protein deacetylase activity, being able to deacetylate lysine residues in non-histone proteins [91] such as microtubules [233], the hsp90 chaperone [281] and the tumour suppressor p53 [322].
Dysregulated HDAC activity has been identified in cancer cells and tumour tissues [305, 444], making HDACs attractive molecular targets in the search for novel mechanisms to treat cancer [567]. Several small molecule HDAC inhibitors are already approved for clinical use: romidepsin, belinostat, vorinostat, panobinostat, belinostat, valproic acid and tucidinostat. HDACs and HDAC inhibitors currently in development as potential anticancer therapeutics are reviewed by Simó-Riudalbas and Esteller (2015) [478].

Information on members of this family may be found in the online database.

Further reading on Histone deacetylases

Maolanon AR *et al.* (2017) Natural and Synthetic Macrocyclic Inhibitors of the Histone Deacetylase Enzymes. *Chembiochem* **18**: 5-49 [PMID:27748555]
Micelli C *et al.* (2015) Histone deacetylases: structural determinants of inhibitor selectivity. *Drug Discov Today* **20**: 718-35 [PMID:25687212]
Millard CJ *et al.* (2017) Targeting Class I Histone Deacetylases in a "Complex" Environment. *Trends Pharmacol Sci* **38**: 363-377 [PMID:28139258]
Roche J *et al.* (2016) Inside HDACs with more selective HDAC inhibitors. *Eur J Med Chem* **121**: 451-83 [PMID:27318122]
Zagni C *et al.* (2017) The Search for Potent, Small-Molecule HDACIs in Cancer Treatment: A Decade After Vorinostat. *Med Res Rev* [PMID:28181261]

3.5.3.15 Peptidyl arginine deiminases (PADI)

Enzymes → 3.5.3.15 Peptidyl arginine deiminases (PADI)

Overview: In humans, the peptidyl arginine deiminases (PADIs; HGNC family link) are a family of five enzymes, PADI1-4 and PADI6. PADIs catalyze the deimination of protein L-arginine residues to L-citrulline and ammonia, generating peptidyl-citrulline on histones, fibrinogen, and other biologically relevant proteins. The human isozymes exhibit tissue-specific expression patterns [256]. Overexpression and/or increased PADI activity is observed in several diseases, including rheumatoid arthritis, Alzheimer's disease, multiple sclerosis, lupus, Parkinson's disease, and cancer [37]. Pharmacological PADI inhibition reverses protein-hypercitrullination and disease in mouse models of multiple sclerosis [366].

Information on members of this family may be found in the online database.

Further reading on Peptidyl arginine deiminases

Koushik S *et al.* (2017) PAD4: pathophysiology, current therapeutics and future perspective in rheumatoid arthritis. *Expert Opin Ther Targets* **21**: 433-447 [PMID:28281906]

Tu R *et al.* (2016) Peptidyl Arginine Deiminases and Neurodegenerative Diseases. *Curr Med Chem* **23**: 104-14 [PMID:26577926]

Whiteley CG. (2014) Arginine metabolising enzymes as targets against Alzheimers' disease. *Neurochem Int* **67**: 23-31 [PMID:24508404]

RAS subfamily

Enzymes → 3.6.5.2 Small monomeric GTPases → RAS subfamily

Overview: The RAS proteins (HRAS, NRAS and KRAS) are small membrane-localised G protein-like molecules of 21 kd. They act as an on/off switch linking receptor and non-receptor tyrosine kinase activation to downstream cytoplasmic or nuclear events. Binding of GTP activates the switch, and hydrolysis of the GTP to GDP inactivates the switch.
The RAS proto-oncogenes are the most frequently mutated class of proteins in human cancers. Common mutations compromise the GTP-hydrolysing ability of the proteins causing constitutive activation [495], which leads to increased cell proliferation and decreased apoptosis [598]. Because of their importance in oncogenic transformation these proteins have become the targets of intense drug discovery effort [25].

Information on members of this family may be found in the online database.

Further reading on RAS subfamily

Dorard C *et al.* (2017) Deciphering the RAS/ERK pathway in vivo *Biochem Soc Trans* **45**: 27-36 [PMID:28202657]

Keeton AB *et al.* (2017) The RAS-Effector Interaction as a Drug Target. *Cancer Res* **77**: 221-226 [PMID:28062402]

Lu S *et al.* (2016) Ras Conformational Ensembles, Allostery, and Signaling. *Chem Rev* **116**: 6607-65 [PMID:26815308]

Ostrem JM *et al.* (2016) Direct small-molecule inhibitors of KRAS: from structural insights to mechanism-based design. *Nat Rev Drug Discov* **15**: 771-785 [PMID:27469033]

Papke B *et al.* (2017) Drugging RAS: Know the enemy. *Science* **355**: 1158-1163 [PMID:28302824]

Quah SY *et al.* (2016) Pharmacological modulation of oncogenic Ras by natural products and their derivatives: Renewed hope in the discovery of novel anti-Ras drugs. *Pharmacol Ther* **162**: 35-57 [PMID:27016467]

Simanshu DK *et al.* (2017) RAS Proteins and Their Regulators in Human Disease. *Cell* **170**: 17-33 [PMID:28666118]

4.2.1.1 Carbonate dehydratases

Enzymes → 4.2.1.1 Carbonate dehydratases

Overview: Carbonic anhydrases facilitate the interconversion of water and carbon dioxide with bicarbonate ions and protons (EC 4.2.1.1), with over a dozen gene products identified in man. The enzymes function in acid-base balance and the movement of carbon dioxide and water. They are targetted for therapeutic gain by particular antiglaucoma agents and diuretics.

Nomenclature	carbonic anhydrase 1	carbonic anhydrase 7	carbonic anhydrase 12
HGNC, UniProt	*CA1*, P00915	*CA7*, P43166	*CA12*, O43570
EC number	4.2.1.1	4.2.1.1	4.2.1.1
Inhibitors	chlorthalidone (pK_i 6.5)	methazolamide (pK_i 8.7) [467], acetazolamide (pK_i 8.6) [19], brinzolamide (pK_i 8.6) [467], chlorthalidone (pK_i 8.6) [524]	chlorthalidone (pK_i 8.4) [524], diclofenamide (pK_i 7.3) [547]

Further reading on 4.2.1.1 Carbonic anhydrases

Frost SC. (2014) Physiological functions of the alpha class of carbonic anhydrases. *Subcell Biochem* **75**: 9-30 [PMID:24146372]
Supuran CT. (2017) Advances in structure-based drug discovery of carbonic anhydrase inhibitors. *Expert Opin Drug Discov* **12**: 61-88 [PMID:27783541]
Supuran CT. (2016) Structure and function of carbonic anhydrases. *Biochem J* **473**: 2023-32 [PMID:27407171]

5.99.1.2 DNA Topoisomerases

Enzymes → 5.99.1.2 DNA Topoisomerases

Overview: DNA topoisomerases regulate the supercoiling of nuclear DNA to influence the capacity for replication or transcription. The enzymatic function of this series of enzymes involves cutting the DNA to allow unwinding, followed by re-attachment to reseal the backbone. Members of the family are targetted in anti-cancer chemotherapy.

Nomenclature	topoisomerase (DNA) I	topoisomerase (DNA) II alpha
HGNC, UniProt	*TOP1*, P11387	*TOP2A*, P11388
EC number	5.99.1.2	5.99.1.2
Inhibitors	irinotecan [125, 518] – Bovine	etoposide (pIC_{50} 7.3), teniposide [127] – Mouse

Further reading on DNA topoisomerases

Bansal S *et al.* (2017) Topoisomerases: Resistance versus Sensitivity, How Far We Can Go? *Med Res Rev* **37**: 404-438 [PMID:27687257]
Capranico G *et al.* (2017) Type I DNA Topoisomerases. *J Med Chem* **60**: 2169-2192 [PMID:28072526]
Nagaraja V *et al.* (2017) DNA topoisomerase I and DNA gyrase as targets for TB therapy. *Drug Discov Today* **22**: 510-518 [PMID:27856347]
Pommier Y *et al.* (2016) Roles of eukaryotic topoisomerases in transcription, replication and genomic stability. *Nat Rev Mol Cell Biol* **17**: 703-721 [PMID:27649880]
Seol Y *et al.* (2016) The dynamic interplay between DNA topoisomerases and DNA topology. *Biophys Rev* **8**: 101-111 [PMID:28510219]

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